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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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☒ Additional inventors are being named on the 1 separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

TIE-2 MODULATORS AND METHODS OF USE

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ENCLOSED APPLICATION PARTS (check all that apply)

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☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-1108 160

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____.

Respectfully submitted,

SIGNATURE Brian D. Griedel Date 4/9/03

TYPED or PRINTED NAME Brian D. Griedel REGISTRATION NO. (if appropriate) 48,425

TELEPHONE 650.837.8326 Docket Number: EX03-023P

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

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PROVISIONAL APPLICATION COVER SHEET
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Docket Number	EX03-023P

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Number 1 of 1

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TIE-2 MODULATORS AND METHODS OF USE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to compounds that inhibit, regulate and/or modulate kinases, particularly Tie-2. Kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above are modulated using compounds of the invention. Methods of using the compounds to treat kinase-dependent diseases and conditions are also an aspect of the invention.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0008] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the

treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0009] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0010] One particularly attractive target for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is Tie-2. Tie-2 (also called TEK) is a member of the receptor tyrosine kinase (RTK) family, which is expressed primarily in endothelial cells and early hemopoietic cells, and plays a critical role in the processes of vasculogenesis and angiogenesis. As such, Tie-2 has been shown to participate in endothelial cell migration, sprouting, survival and periendothelial cell recruitment during angiogenesis.

[0011] The angiopoietin family of growth factors regulates Tie-2 activity through a combination of agonistic and antagonistic extracellular ligands. Binding of the ligands, Angiopoietin-1 (Ang-1) or Ang-4 by Tie-2 induces autophosphorylation resulting in an increase of receptor dependent signaling, while binding to Ang-2 and Ang-3 results in down regulation of receptor activity. Ang-1 signaling through Tie-2 facilitates later stages of vascular development by modulating cell-cell, and cell-matrix interactions, resulting in the survival and stabilization of newly formed blood vessels.

[0012] Tumor growth progression requires the recruitment of new blood vessels into the tumor from preexisting vessels. Accordingly, Tie-2 expression has been demonstrated on a wide variety of tumor types including ovarian, breast, renal, prostate, lung, thyroid, myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Tie-2 activation has also been linked to venous malformations (VM), the most common form of vascular morphogenesis in humans. As well, an activating mutation in the kinase domain of Tie-2 occurs in multiple families who exhibit a dominantly inherited form of VM. Tie-2 has been linked to multiple cancer types, including ovarian, breast, renal, prostate, lung, thyroid,

myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas (See: Shirkawa et al Int J Cancer 2002 Jun 20; 99(6):821-8; Tanka et al Clin Cancer Res 2002 May;8(5):1125-31; Mitsutake et al Thyroid 2002 Feb; 12(2):95-9; Muller et al Leuk Res 2002 Feb; 26(2):163-8; Yu et al Am J Pathol 2001 Dec; 159(6):2271-80; Pomyje et al Melanoma Res 2001 Dec; 11(6):639-43; Harris et al Clin Cancer Res 2001 Jul;7(7):1992-7; Wrumback et al Anticancer Res 2000 Nov-Dec;20(6D):5217-20; Ding et al Deuro-oncol 2001 Jan;3(1):1-10; Takahama et al Clin Cancer Res 1999 Sep;5(9):2506-10; Stratmann et al Am J Pathol 1998 Nov;153(5):1549-66; and, Kukk et al Br J Haematol 1997 Jul;98(1):195-203). Additionally, activation of Tie-2 has been linked to the vascular dysmorphogenesis syndrome, venous malformation (See: Vikkula et al Cell 1996 Dec;87(1):1181-1190). Thus modulation of Tie-2 is desirable as a means to treat cancer and cancer-related disease.

[0013] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly Tie-2, is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis, and is an object of this invention.

SUMMARY OF THE INVENTION

[0014] The present invention provides compounds for modulating kinase activity and methods of treating diseases mediated by kinase activity, in particular Tie-2, utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by kinase activity are from herein referred to as "kinase-dependent diseases or conditions" (see definition in detailed description of invention below). Inhibitors that are selective for a Tie-2 are included in this invention.

[0015] In another aspect, the invention provides methods of screening for modulators of kinase activity. The methods comprise combining a composition of the invention, a kinase, and at least one candidate agent and determining the effect of the candidate agent on the kinase activity.

[0016] In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical compounds and/or compositions of the present invention, including, one or more kinase enzyme activity

modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

[0017] In still yet another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

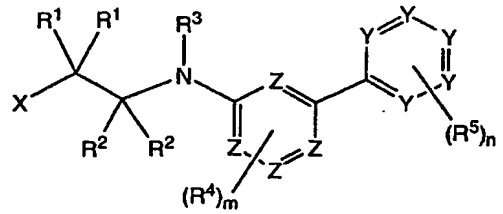
[0018] These and other features and advantages of the present invention will be described in more detail below.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as atherosclerosis, myocardioinfarction, ischemia, pulmonary hypertension, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0020] It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally," but proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

[0021] The present invention comprises compounds for modulating kinase activity, particularly Tie-2, of Formula I,

I 

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

X is selected from -H, $-OR^6$, $-SR^6$, $-N(R^6)R^7$, absent, oxo, thiono, and imino, with the proviso that when X is oxo, thiono, or imino, there is only one R^1;

R^1 and R^2 are each independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and absent;

optionally two of R^2 together are oxo;

optionally, at least one pair of substituents, selected from two of R^1, two of R^2, and one each of R^1 and R^2, together with the corresponding carbon or carbons to which they are attached, form a first ring system comprising between 3 and 7 ring atoms, said first ring system optionally substituted with between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the first ring system to which they are attached, form a second ring system comprising between 3 and 7 ring atoms, said second ring system optionally substituted with between 0 and 3 of R^1;

R^3 is selected from -H, optionally substituted lower alkyl, optionally substituted lower arylalkyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted alkoxy; or

R^3 and one of R^2, together with the atoms to which each is attached, form a third ring system comprising between 3 and 7 ring atoms, said third ring system optionally substituted with between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the third ring

system to which they are attached, form a fourth ring system comprising between 3 and 7 ring atoms, said fourth ring system optionally substituted with between 0 and 3 of R^1; or

R^3 and one of R^1, together with the atoms to which they are attached and the carbon to which R^2 is attached, form a fifth ring system comprising between 3 and 7 ring atoms atoms, said fifth ring system optionally substituted with between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the fifth ring system to which they are attached, form a sixth ring system comprising between 3 and 7 ring atoms, said sixth ring system optionally substituted with between 0 and 3 of R^1;

m is 0 to 4;

R^4 is independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl;

optionally two adjacent R^4's, together with the two carbons to which they are attached, form a seventh ring system fused with the aromatic ring system to which said two adjacent R^4's are attached as in formula I, said seventh ring system comprising between 5 and 7 atoms and substituted with 0 to 3 additional of R^4, provided said seventh ring system when fused with the aromatic ring system to which said two adjacent R^4's are attached does not constitute a 7-deazapurine;

each Y is independently either $=C(R^5)-$ or =N-, provided that there are no more than 3 of =N- in the aromatic ring bearing Y;

each Z is independently either $=C(R^4)-$ or =N-;

n is 0 to 4;

R^5 is independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower

arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; and

optionally two adjacent R^5's, together with the two carbons to which they are attached, form an eighth ring system fused with the aromatic ring system to which said two adjacent R^5's are attached as in formula I, said eighth ring system comprising between 5 and 7 atoms and substituted with 0 to 3 additional of R^5;

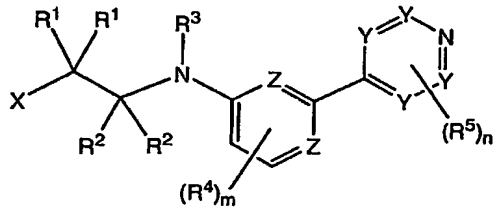
R^6 is -H or R^7; and

R^7 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

R^6 and R^7, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl ring, said optionally substituted five- to seven-membered heterocyclyl ring optionally containing at least one additional heteroatom selected from N, O, S, and P.

[0022] In one example, the compounds are according to paragraph [0021], of formula **II**,

II

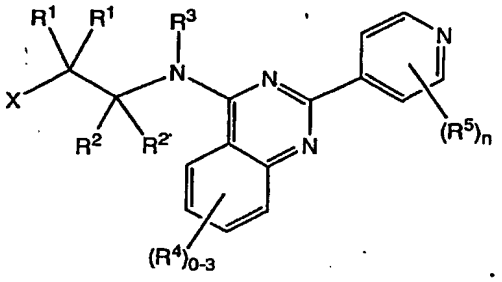


[0023] In another example, the compounds are according to paragraph [0022], wherein at least one of Z is –N=.

[0024] In another example, the compounds are according to paragraph [0022], wherein Z is -N=.

[0025] In another example, the compounds are according to paragraph [0024], wherein Y is $=C(R^5)-$.

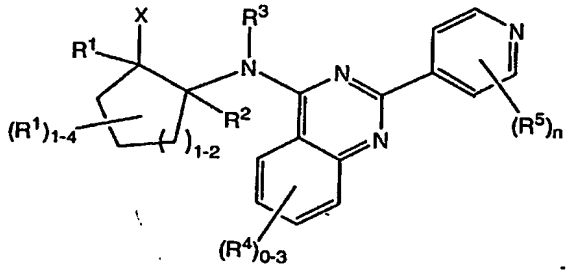
[0026] In another example, the compounds are according to paragraph [0025], of formula III,

III 

[0027] In another example, the compounds are according to paragraph [0026], wherein one each of R^1 and R^2, together with the corresponding carbons to which they are attached, form said first ring system, said first ring system comprising a saturated ring, said saturated ring optionally substituted with between 0 and 4 additional of R^1.

[0028] In another example, the compounds are according to paragraph [0027], wherein said saturated ring is carbocyclic.

[0029] In another example, the compounds are according to paragraph [0028], of formula IV

IV 

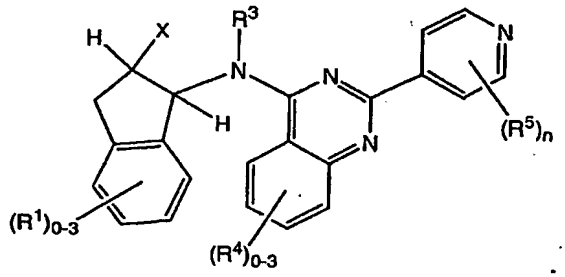
[0030] In another example, the compounds are according to paragraph [0029], wherein X is selected from $-OR^6$, $-SR^6$, and $-N(R^6)R^7$.

[0031] In another example, the compounds are according to paragraph [0030], wherein two of R^1, together with the carbon or carbons to which they are attached, form said second ring system.

[0032] In another example, the compounds are according to paragraph [0031], wherein said second ring system is a six-membered aryl ring system, fused with said first ring system, said second ring system optionally substituted with between 0 and 3 of R^1.

[0033] In another example, the compounds are according to paragraph [0032], of formula **V**,

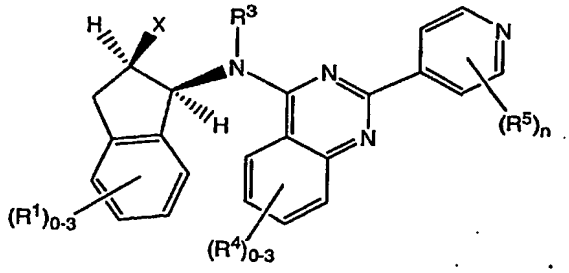
V



[0034] In another example, the compounds are according to paragraph [0033], wherein X is $-OR^6$.

[0035] In another example, the compounds are according to paragraph [0034], of formula **VI**,

VI

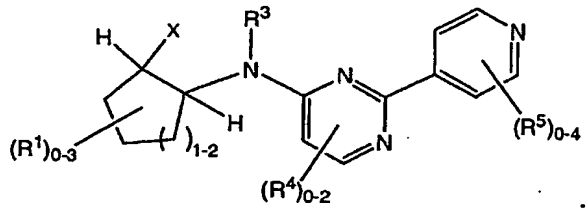


[0036] In another example, the compounds are according to paragraph [0035], wherein R^3 is -H.

[0037] In another example, the compounds are according to paragraph [0036], wherein X is -OH.

[0038] In another example, the compounds are according to paragraph [0037], wherein R^1, R^4, and R^5 are -H.

[0039] In another example, the compounds are according to paragraph [0025], of formula **VII**,

VII 

[0040] In another example, the compounds are according to paragraph [0039], wherein X is selected from $-OR^6$, $-SR^6$, and $-N(R^6)R^7$.

[0041] In another example, the compounds are according to paragraph [0040], wherein X is -OH.

[0042] In another example, the compounds are according to paragraph [0041], wherein R^3 is -H.

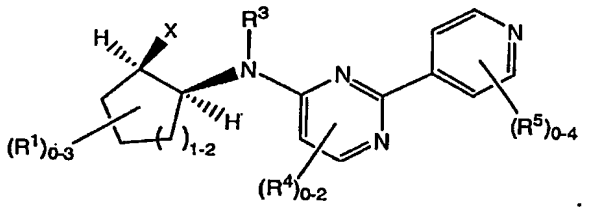
[0043] In another example, the compounds are according to paragraph [0042], wherein at least one of R^1 is an optionally substituted aryl.

[0044] In another example, the compounds are according to paragraph [0042], wherein at least one of R^4 is an optionally substituted aryl.

[0045] In another example, the compounds are according to paragraph [0042], wherein at least one of R^1 is an optionally substituted phenyl.

[0046] In another example, the compounds are according to paragraph [0042], wherein at least one of R^4 is an optionally substituted phenyl.

[0047] In another example, the compounds are according to paragraph [0042], of formula VIII,

VIII 

[0048] In another example, the compounds are according to paragraph [0040], wherein two R^4's, together with the aromatic ring atoms to which they are attached, form said seventh ring system, said seventh ring system comprising between 0 and 2 nitrogens.

[0049] In another example, the compounds are according to paragraph [0048], wherein said seventh ring system is substituted with between 0 and 3 additional of R^4.

[0050] In another example, the compounds are according to paragraph [0021], selected from the compounds in Table 1.

Table 1

#	Name
1	N-cyclohexyl-2-pyridin-4-ylquinazolin-4-amine
2	2-pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)quinazolin-4-amine
3	N-cyclopentyl-2-pyridin-4-ylquinazolin-4-amine
4	N-(cyclohexylmethyl)-2-pyridin-4-ylquinazolin-4-amine
5	2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
6	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
7	N-[(4-fluorophenyl)methyl]-2-pyridin-4-ylquinazolin-4-amine
8	N,N-dimethyl-N'-(2-pyridin-4-ylquinazolin-4-yl)ethane-1,2-diamine
9	N-(2,3-dihydro-1H-inden-1-yl)-2-pyridin-4-ylquinazolin-4-amine
10	N-(2-morpholin-4-ylethyl)-2-pyridin-4-ylquinazolin-4-amine
11	4-[4-(2-pyridin-4-ylquinazolin-4-yl)piperazin-1-yl]phenol
12	2-pyridin-4-yl-N-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine
13	4-piperazin-1-yl-2-pyridin-4-ylquinazoline
14	1,1-dimethylethyl 4-(2-pyridin-4-ylquinazolin-4-yl)piperazine-1-carboxylate
15	2-pyridin-4-yl-N-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine
16	4-[(1S)-2,3-dihydro-1H-inden-1-ylmethyl]-2-pyridin-4-ylquinazoline

#	Name
17	(1R,2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
18	(1S,2R)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
19	1,1-dimethylethyl 4-[(2-pyridin-4-ylquinazolin-4-yl)amino]piperidine-1-carboxylate
20	2-pyridin-4-yl-N-{[2,4,6-tris(methyloxy)phenyl]methyl}quinazolin-4-amine
21	N-piperidin-4-yl-2-pyridin-4-ylquinazolin-4-amine
22	N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}-2-pyridin-4-ylquinazolin-4-amine
23	N-phenyl-N'-(2-pyridin-4-ylquinazolin-4-yl)benzene-1,4-diamine
24	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]naphthalen-2-ol
25	N-{4-[(1-methylethyl)oxy]phenyl}-2-pyridin-4-ylquinazolin-4-amine
26	(1S,2R)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
27	(1R,2S)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
28	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclopentanol
29	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclohexanol
30	(1S,2R,3R,5R)-3-(hydroxymethyl)-5-[(2-phenylquinazolin-4-yl)amino]cyclopentane-1,2-diol
31	(1S,2R)-1-[(6-chloro-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
32	N-(2-piperazin-1-ylethyl)-2-pyridin-4-ylquinazolin-4-amine
33	(1S,2R)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
34	(1R,2S)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
35	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclopentanol
36	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclohexanol

#	Name
37	(1S,2R)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
38	(1R,2S)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
39	(2S)-3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propane-1,2-diol
40	[(2S)-1-(2-pyridin-4-ylquinazolin-4-yl)-2,3-dihydro-1H-indol-2-yl]methanol
41	(2R)-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
42	(2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-2-ol
43	(1S,2R)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
44	(1R,2S)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
45	(1S,2R)-1-[(6-bromo-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
46	(1S,2R)-1-{[6,7-bis(methyloxy)-2-pyridin-4-ylquinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
47	1-(2-pyridin-4-ylquinazolin-4-yl)piperidin-3-ol
48	(1S,2R)-1-{[2-pyridin-4-yl-7-(trifluoromethyl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
49	(1S,2R)-1-({2-[6-(methyloxy)pyridin-3-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol
50	N-[(3S)-piperidin-3-yl]-2-pyridin-4-ylquinazolin-4-amine
51	(1S,2R)-1-[(7-methyl-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
52	(1S,2R)-1-({2-[2,4-bis(methyloxy)pyrimidin-5-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol
53	(2R)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol
54	(2S)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol
55	(2S)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
56	(2R)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol

#	Name
57	(1S,2R)-1-[(2-pyridin-4-ylpyrimidin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
58	(1S,2R)-1-[(2-pyrazin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
59	(1S,2R)-1-{[2-(4-aminopyridin-3-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
60	(2R)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
61	(2S)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
62	2-[(phenylmethyl)(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
63	(1S,2R)-1-{[2-(2-aminopyrimidin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
64	5-(4-{[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}quinazolin-2-yl)pyridin-2-ol
65	(1S,2R)-1-({2-[2-(methylthio)pyrimidin-4-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol

[0051] Another aspect of the invention is a pharmaceutical composition comprising a compound according to any one of paragraphs 21-50 and a pharmaceutically acceptable carrier.

[0052] Another aspect of the invention is a metabolite of a compound or the pharmaceutical composition according to any one of paragraphs 21-51.

[0053] Another aspect of the invention is a method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to paragraph [0051].

[0054] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the pharmaceutical composition according to paragraph [0051].

[0055] Another aspect of the invention is a method according to paragraph [0054], wherein the kinase is Tie-2.

[0056] Another aspect of the invention is a method according to paragraph [0055], wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

Definitions

[0057] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0058] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to eight carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, isobutyl, pentyl, hexyl, cyclohexyl, and the like. Higher alkyl refers to alkyl groups containing more that 6 carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus either "butyl" or "C_4alkyl" is meant to include n-butyl, sec-butyl, isobutyl, t-butyl, isobutenyl and but-2-yne radicals, for example; "propyl" or "C_3alkyl" each include n-propyl, propenyl, and isopropyl, for example. Alkyls with variable numbers of carbons may be named by using number ranges as subscripts, as for example, lower alkyl is equivalent to $C_{1\text{-}8}$alkyl.

[0059] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, e.g., methylene, ethylene, propylene, n-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically fully saturated. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene

($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$) and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[0060] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, e.g., ethylidene, propylidene, n-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically double bond unsaturation. The unsaturation present includes at least one double bond and a double bond can exist between the first carbon of the chain and a carbon atom of the rest of the molecule to which it is attached.

[0061] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, e.g., propylid-2-ynyl, n-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically triple bond unsaturation. The unsaturation present includes at least one triple bond and a triple bond can exist between the first carbon of the chain and a carbon atom of the rest of the molecule to which it is attached.

[0062] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an n-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0063] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0064] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O- (optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of

between about 2 and about 20, in another example, between about 2 and about 10, and in a further example between about 2 and about 5. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is for example an integer of between about 1 and about 10, in another example y is an integer of between about 1 and about 4. Thus, where a group is defined as -OR, where "R" is optionally substituted alkyl, then such a group would include, but not be limited to, hydroxyalkoxy, polyalkoxy, and the like.

[0065] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0066] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

[0067] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -NHR or -NRR where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, e.g., diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

[0068] "Aryl" refers to aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, fluorene and the like.

[0069] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. The aryl, alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to eight carbons.

[0070] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. Dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0071] "Heteroatom" refers to O, S, N, or P.

[0072] "Heterocyclyl" refers to a stable 3- to 15-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, either aromatic, saturated, or combinations thereof; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl ring radical may be optionally oxidized to various oxidation states, for example for the purposes of this invention and to negate undo repetition in the description, the corresponding N-oxide of pyridine derivatives, and the like, are understood to be included as compounds of the invention. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclyl ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl,

indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0073] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl ring system radical.

[0074] "Heteroaryl" refers specifically to an aromatic heterocyclyl ring system radical.

[0075] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl ring is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. The heterocyclyl, alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to eight carbons.

[0076] The term "imino" refers to a substitution on a carbon atom, more specifically to a doubly bonded nitrogen. For example, an imine, an amidine, and an oxime, all contain the "imino" group.

[0077] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*) that are sterically impractical and/or synthetically non-feasible. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted C_{1-8}alkylaryl," optional substitution may occur on both the "C_{1-8}alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted

alkyl groups, potentially *ad infinitum*. If a hetercyclic ring is "optionally substituted," then both the carbon and any heteroatoms in the ring may be substituted thereon. Examples of optional substitution include, but are not limited to alkyl, halogen, alkoxy, hydroxy, oxo, carbamyl, acylamino, sulfonamido, carboxy, alkoxycarbonyl, acyl, alkylthio, alkylsulfonyl, nitro, cyano, amino, alkylamino, cycloalkyl and the like. Thus, for example, if a group "-C(O)R" is described, where "R" is optionally substituted alkyl, then "R" would include, but not be limited to, $-CH_2Ph$, $-CH_2CH_2OPh$, $-CH{=}CHPhCH_3$, $-C_3H_4CH_2N(H)Ph$, and the like.

[0078] The term "ortho" is normally used in reference to relative position of two substituents on a benzene ring; however, in this application the term "ortho" is meant to apply to other aromatic ring systems where two substituents reside on adjacent carbons. For example, 3-bromo-4-fluoro-thiophene possesses a bromo group and a fluoro group which have an ortho, or 1,2-positional relationship, to each other.

[0079] The term "oxo" refers to a substitution on a carbon atom, more specifically to a doubly bonded oxygen. For example, an oxo-morpholine, a cyclohexanone, and an acyl group, all contain the "oxo" functionality.

[0080] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about 5, in another example, up to about 3) hydrogen atoms are replaced by a substituent independently selected from the group: optionally substituted alkyl (e.g., fluoroalkyl), optionally substituted alkoxy, alkylenedioxy (e.g. methylenedioxy), optionally substituted amino (e.g., alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryl (e.g., phenyl), optionally substituted arylalkyl (e.g., benzyl), optionally substituted aryloxy (e.g., phenoxy), optionally substituted arylalkyloxy (e.g., benzyloxy), carboxy (-COOH), carboalkoxy (i.e., acyloxy or -OOCR), carboxyalkyl (i.e., esters or -COOR), carboxamido, aminocarbonyl, benzyloxycarbonylamino (CBZ-amino), cyano, carbonyl, halogen, hydroxy, optionally substituted heterocyclylalkyl, optionally substituted heterocyclyl, nitro, sulfanyl, sulfinyl, sulfonyl, and thio.

[0081] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0082] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0083] "Sulfonyl" refers to the groups: -S(O_2)-H, -S(O_2)-(optionally substituted alkyl), -S(O_2)-optionally substituted aryl), -S(O_2)-(optionally substituted heterocyclyl), -S(O_2)-(optionally substituted alkoxy), -S(O_2)-optionally substituted aryloxy), and -S(O_2)-(optionally substituted heterocyclyloxy).

[0084] The term "thiono" refers to a substitution on a carbon atom, more specifically to a doubly bonded sulfur. For example, a thioketone and a thioamide both contain the "thiono" functionality.

[0085] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0086] In some embodiments, as will be appreciated by those in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) may contain two substitution groups.

[0087] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl ring systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0088] Compounds of the invention are generally named using ACD/Name (available from Advanced Chemistry Development, Inc. of Toronto, Canada). This software derives names from chemical structures according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0089] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

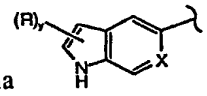
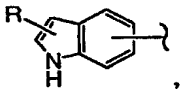
[0090] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

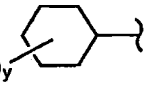
[0091] When a particular group with its bonding stucture is denoted as being bonded to two partners, e.g. $-OCH_2-$, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group.

[0092] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When desired, the R- and S-isomers may be resolved by methods known to those skilled in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0093] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, and "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached. When a group is depicted

removed from its parent formula, the "~" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[0094] When a group "R" is depicted as existing on a fused ring system, as for example in the formula  , then a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted (e.g. the -NH- in the formula above), implied (e.g. as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (e.g. where in the formula above, "X" equals -CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring. When there are more than one such depicted "floating" groups, as for example in the formula  , where there are two groups, namely, the "R" and the bond indicating attachment to a parent structure. In such cases, the "floating" groups may reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

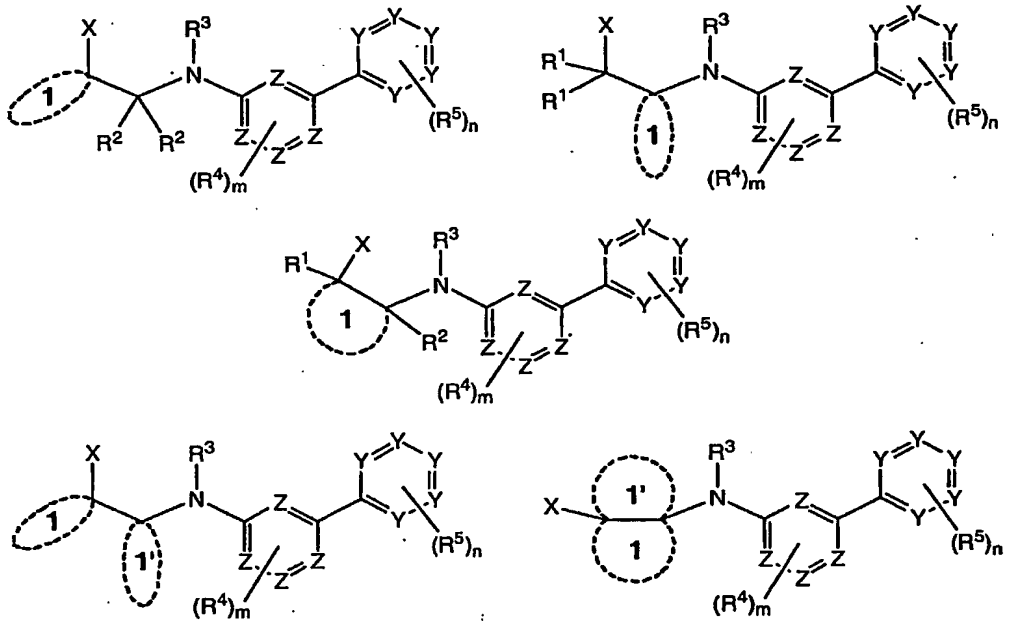
[0095] When a group "R" is depicted as existing on a saturated ring system, as for example in the formula  where "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring, then where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group, then in this instance there would exist a geminal dimethyl on a carbon of the depicted ring. In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring structure with the depicted ring.

[0096] As described in paragraph [0021], R^1, R^2, and R^3 of formula I can, in specified paired combinations, form ring systems (designated ring one through ring six). As well, the central and distal aromatic rings depicted in formula I may themselves have rings fused thereto (designated as ring seven and ring eight, respectively). Rings systems one, two, four, and six

may be aromatic, saturated, or partially saturated; ring systems three and five are at least partially saturated. To orient the reader to what is meant by these ring designations, a few examples (schemes and corresponding description) are provided below.

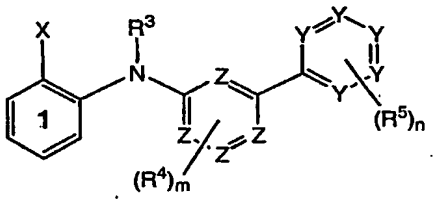
[0097] As mentioned, optionally at least one pair of substituents from formula I selected from two of R^1, two of R^2, and one each of R^1 and R^2, together with the atoms to which they are attached, may form a first ring system. Using formula I as a guide, such a first ring system (designated as ring "1" or "1'") is depicted schematically below. Ring 1 may take any of the forms as depicted below in Scheme 1. Consistent with the description above, there can be more than one ring 1 (since there are two each of R^1 and R^2 in formula I), as depicted in the last two ring schemes.

Scheme 1

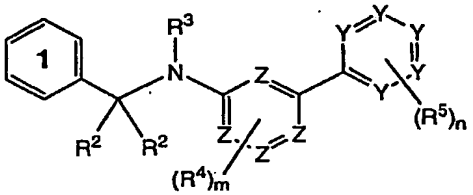


[0098] It is understood by one skilled in the art, that depending on whether or not a ring system is aromatic or contains at least one unit of unsaturation (e.g. double or triple bond), then at least one of substituents, X, R^1, and R^2, may be absent in a compound of the invention. For example according to formula I, if one each of R^1 and R^2, together with the carbons to which they are attached, form an aromatic ring system, 1, then at least other two

substituents, R^2 and at least one of X and R^1, are understood to be absent, for example as depicted in formula (i) below. In another example according to formula **I**, if both R^1's, together with the carbon to which they are attached, form a phenyl ring, then X is understood to be absent, as in formula (ii) below (if such a ring is aliphatic or otherwise does not require sp^2 hybridization at the carbon to which X is attached, then X is present). In no case can both R^2 (as depicted in formula **I**), together with the carbon to which they are attached, form an aromatic ring.



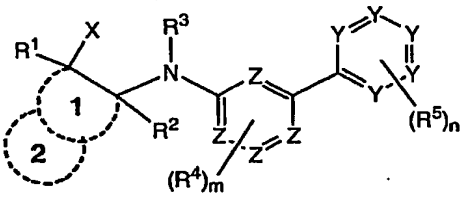
(i)

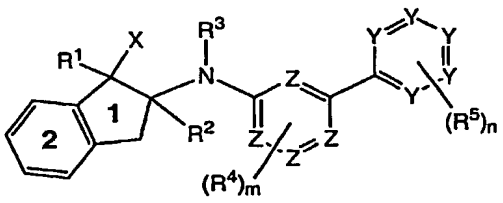


(ii)

[0099] Also as described above, ring systems one, three, and five may have an additional ring system attached thereto. This additional ring may be attached to form a spiro- bicyclic ring system, a bridged bicyclic system, or fused ring system. Thus for example, any of rings, **1** (or **1'**), depicted in Scheme 1, may themselves have a ring, **2**, attached. An exemplary ring scheme for such a structure is depicted in Scheme 2, along with a corresponding more specific formulation (iii), neither are meant to be limiting to scope of the invention. As described, both rings **1** and **2** may also have additional substitution thereon. The more specific formulation (iii) shows ring **1** as saturated and ring **2** as aromatic.

Scheme 2



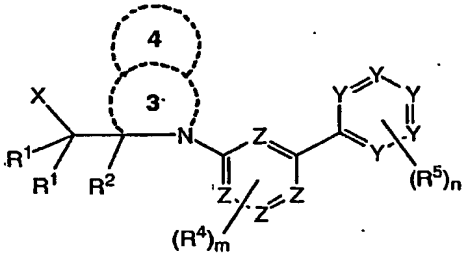


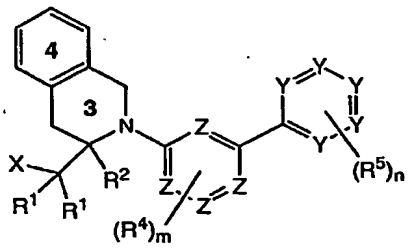
(iii)

[0100] Scheme 3 depicts two ring schemes (and corresponding more specific formulations, (iv) and (v)) for ring systems 3 and 5 as described and according formula **I**, with analogous

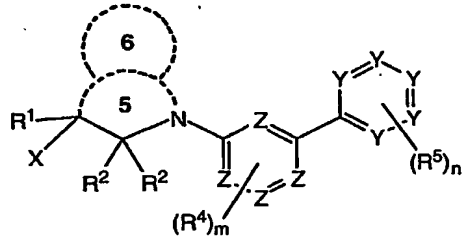
attached ring systems 4 and 6, respectively. As in Scheme 2, only fused rings are depicted, although spiro- systems are meant to be within the scope of the invention.

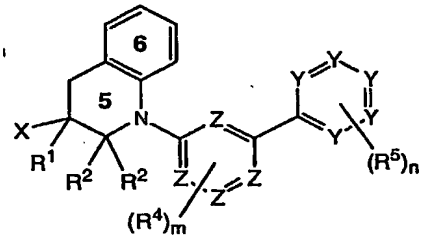
Scheme 3





(iv)

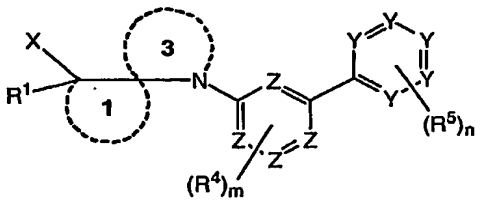


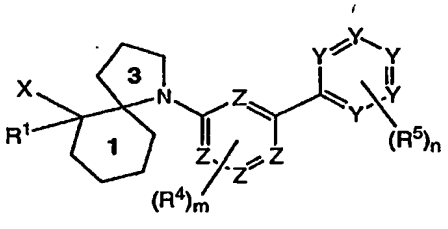


(v)

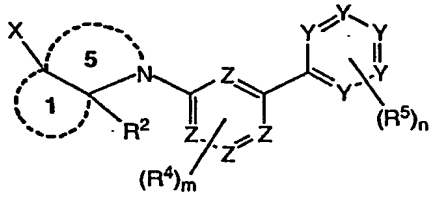
[0101] Scheme 4 depicts two ring schemes (and corresponding more specific formulae, (vi) and (vii)), showing that compounds of the invention can, consistent with the description herein, comprise combinations of the above described ring systems. In one example, there is a first ring system, **1**, and a third ring system, **3**. In the other example, there is a first ring system, **1**, and a fifth ring system, **5**.

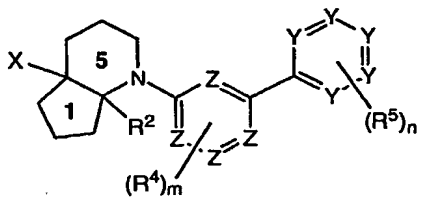
Scheme 4





(vi)





(vii)

[0102] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0103] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion.

[0104] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases. That is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. Thus, "kinase-dependent diseases or conditions" are those diseases that should be mitigated via treatment of a patient with compounds and/or formulations of the invention. Kinase-dependent diseases or conditions include diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), the pathologic neovascularization that supports solid tumor growth, programmed cell death (apoptosis), diseases associated with dysregulated vascularization, cell migration and invasion and angiogenesis associated with tumor growth. In addition to oncological diseases, kinase-dependent diseases, include but are not limited to, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Thus specific kinase-dependent diseases include, but are not limited to, cancer (see definition below),

rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; atheroslerosis, myocardioinfarction, ischemia, stroke and restenosis, interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy, and endometriosis.

[0105] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0106] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous

system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0107] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0108] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary,

secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0109] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about 1 and about 6 carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about 1 and about 6 carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. Another example of a prodrug is a pyridine group; in many cases the pyridine group is oxidized to its corresponding N-oxide that may be a biologically active compound of the invention. Thus the "pyridine form"may be thought of as a prodrug. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0110] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; e.g., biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or

to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0111] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0112] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0113] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

General Administration

[0114] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar

utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0115] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0116] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0117] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0118] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0119] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0120] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0121] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn

germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0122] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0123] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0124] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0125] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0126] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0127] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to those skilled in the art.

Utility of compounds of the invention as screening agents

[0128] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example a Tie-2 receptor kinase, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0129] The determination of the binding of the candidate agent to, for example, a Tie-2 protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion

of the Tie-2 protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0130] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0131] In some embodiments, only one of the components is labeled. For example, a Tie-2 protein may be labeled at tyrosine positions using ^{125}I, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0132] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to Tie-2's.

[0133] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 and less than about

2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0134] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0135] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to Tie-2's, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0136] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to a Tie-2 for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C.

[0137] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is

then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0138] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to a Tie-2 and thus is capable of binding to, and potentially modulating, the activity of the Tie-2. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0139] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to a Tie-2 with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to a Tie-2.

[0140] It may be of value to identify the binding site of a Tie-2. This can be done in a variety of ways. In one embodiment, once a Tie-2 has been identified as binding to the candidate agent, the Tie-2 is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0141] Modulation is tested by screening for candidate agents capable of modulating the activity of Tie-2's comprising the steps of combining a candidate agent with a Tie-2, as above, and determining an alteration in the biological activity of the Tie-2. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphorlogy, and the like.

[0142] Alternatively, differential screening may be used to identify drug candidates that bind to native Tie-2's, but cannot bind to modified Tie-2's.

[0143] Positive controls and negative controls may be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the

protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

[0144] A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

Abbreviations and their Definitions

[0145] The following abbreviations and terms have the indicated meanings throughout:

Ac	=	acetyl
ATP	=	adenosine triphosphate
BNB	=	4-bromomethyl-3-nitrobenzoic acid
Boc	=	t-butyloxy carbonyl
br	=	broad
Bu	=	butyl
C	=	degrees Celsius
c-	=	cyclo
CBZ	=	carbobenzoxy = benzyloxycarbonyl
d	=	doublet
dd	=	doublet of doublet
dt	=	doublet of triplet
DBU	=	diazabicyclo[5.4.0]undec-7-ere
DCM	=	dichloromethane = methylene chloride = CH_2Cl_2
DCE	=	dichloroethylene
DEAD	=	diethyl azodicarboxylate
DIC	=	diisopropylcarbodiimide

DIEA	=	N,N-diisopropylethyl amine
DMAP	=	4-N,N-dimethylaminopyridine
DMF	=	N,N-dimethylfonnamide
DMSO	=	dimethyl sulfoxide
DVB	=	1,4-divinylbenzene
EEDQ	=	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	=	Electron Impact ionization
Et	=	ethyl
Fmoc	=	9-fluorenylmethoxycarbonyl
g	=	gram(s)
GC	=	gas chromatography
h or hr	=	hour(s)
HATU	=	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	=	hexamethyldisilazane
HOAc	=	acetic acid
HOBt	=	hydroxybenzotriazole
HPLC	=	high pressure liquid chromatography
L	=	liter(s)
M	=	molar or molarity
m	=	multiplet
Me	=	methyl
mesyl	=	methanesulfonyl
mg	=	milligram(s)
MHz	=	megahertz (frequency)
min	=	minute(s)
mL	=	milliliter(s)
mM	=	millimolar
mmol	=	millimole(s)
mol	=	mole(s)
MS	=	mass spectral analysis

MTBE	=	methyl t-butyl ether
N	=	normal or normality
NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
nM	=	nanomolar
NMO	=	N-methylmorpholine oxide
NMR	=	nuclear magnetic resonance spectroscopy
PEG	=	polyethylene glycol
pEY	=	poly-glutamine, tyrosine
Ph	=	phenyl
PhOH	=	phenol
PfP	=	pentafluorophenol
PfPy	=	pentafluoropyridine
PPTS	=	pyridinium p-toluenesulfonate
Py	=	pyridine
PyBroP	=	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	=	quartet
RT	=	room temperature
Sat'd	=	saturated
s	=	singlet
s-	=	secondary
t-	=	tertiary
t or tr	=	triplet
TBDMS	=	t-butyldimethylsilyl
TES	=	triethylsilane
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMOF	=	trimethyl orthoformate
TMS	=	trimethylsilyl
tosyl	=	p-toluenesulfonyl
Trt	=	triphenylmethyl

uL	=	microliter(s)
uM	=	micromole(s) or micromolar

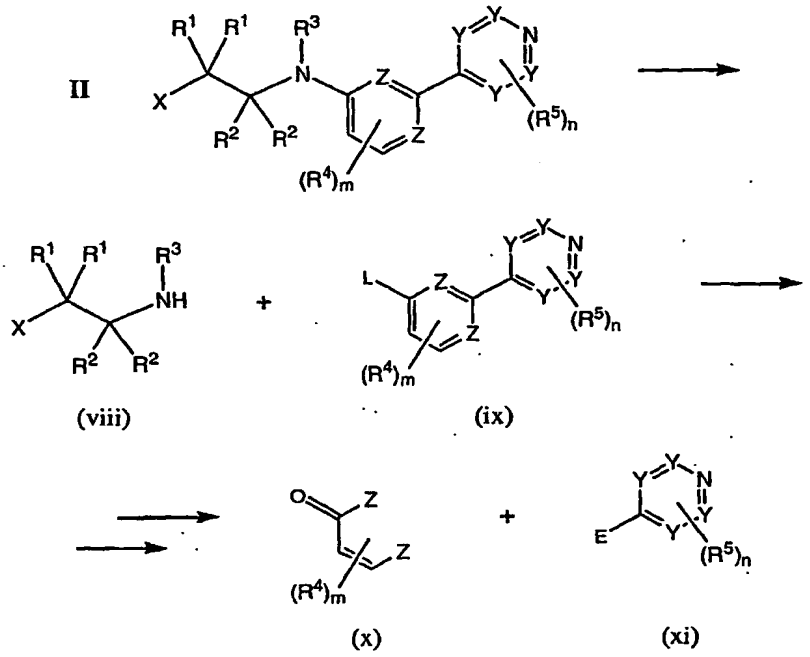
Synthesis of Compounds

[0146] Scheme 5 depicts a general synthetic route for exemplary compounds of the invention and is not intended to be limiting. Specific examples are described subsequently to this general synthetic description. In the generalizations below, specific reaction conditions, for example, added bases, acids, solvents, temperature, and the like are not described so as not to confuse the discussion. The general route, in conjunction with the specific examples, contains sufficient information to allow one skilled in the art to synthesize compounds of the invention.

[0147] Scheme 5 is presented as a retrosynthetic analysis. In this scheme, some substituents (e.g. X and R^1 through R^5) are not defined described as taking part in the synthesis of compounds of the invention. This is done purely for simplification of description of synthesis in general. Such substituents may be appended to the scaffold of depicted formulae at any time during synthesis or may pre-exist on intermediates or starting materials used to make compounds of the invention, as would be understood by one skilled in the art. More specific examples are presented below to more fully describe the invention.

[0148] Again referring to Scheme 5, compounds of formula **II**, for example, are made generally by coupling of an amine (viii) with a bis-aryl intermediate (ix). Intermediate (ix) has a leaving group, "L"; the amine function of (viii) acts as a nucleophile to ultimately displace L from the ring bearing "Z" of intermediate (ix). Intermediate (ix) is generally made by formation of the ring bearing Z via coupling and condensation of (x) with (xi). An electrophilic group "E" coupled with nucleophilic groups Z and condensation/ring formation, followed by introduction of L ultimately via the carbonyl of (x), gives (ix). Of course, one skilled in the art would understand that depending on the nature of Z and E, other reaction types and routes are available to make (ix). In some cases, intermediate (ix) is commercially available, or the aryl rings of (ix), pre-existing, are coupled via aromatic coupling reactions.

Scheme 5

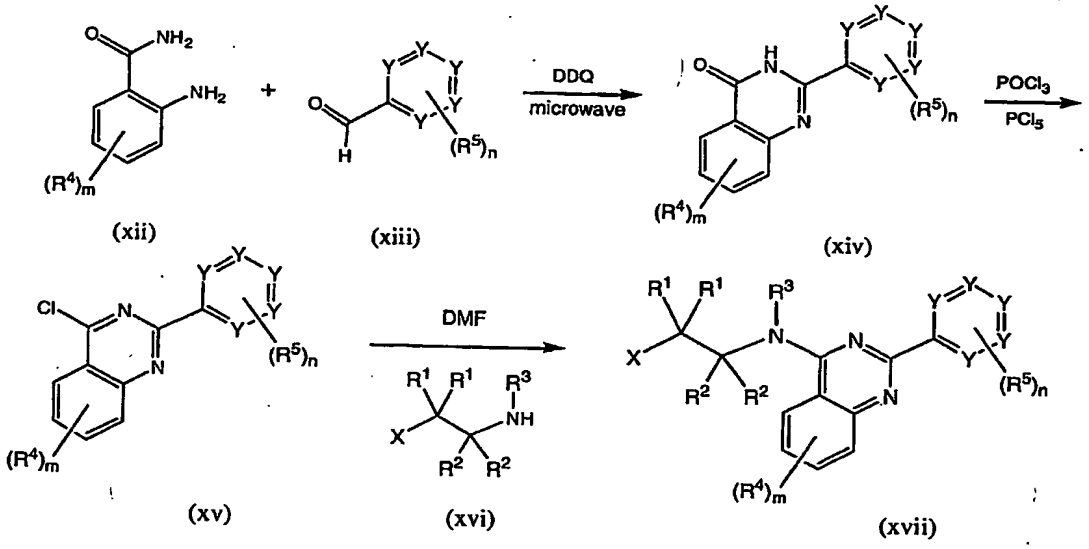


Examples

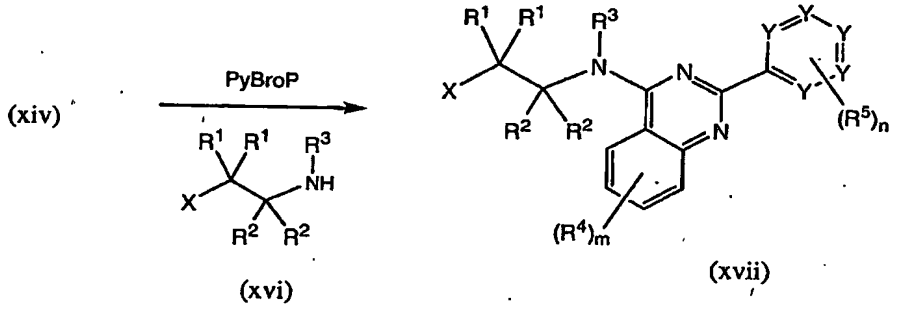
[0149] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, each example is set out below with a corresponding multi-step synthesis scheme. Following specific examples are lists of compounds that were made in a similar way. Scheme 6 depicts synthesis of quinazolines (xvii) according to Formula I. Generally, an optionally substituted anthranilamide (xii) is coupled with an optionally substituted aromatic aldehyde (xiii) to make intermediate (xiv). Intermediate (xiv) is converted to the corresponding 4-chloroquinazoline (xv), which is coupled with amine (xvi) to form 4-amino quinazoline (xvii). Again, in some instances, substituents X and R^1 through R^5 can be introduced at any

stage of the synthesis. Scheme 7 shows that, alternatively, intermediate (xiv) can be converted to (xvii) in a "one pot" reaction using bromo-tris-pyrrolidino-phosphonium hexafluorophosphate.

Scheme 6



Scheme 7



Example 1

[0150] 2-Pyridin-4-ylquinazolin-4(3H)-one: To a flask of anthranilamide (1 mmol) was added 4-pyridine carboxaldehyde (1 mmol) to form a paste. Followed by the careful addition

of 2,3 dichloro-5,6-dicyano-1,4-benzoquinone, (0.5 mmol), the well blended mixture was microwaved in a beaker with silica for 9 min. To the resultant solid was added methanol with subsequent sonication. The collected filtrate was concentrated and dried *in vacuo* to afford the desired product as a brown solid (85% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.80 (br s, 1H), 8.80 (d, 2H), 8.20 (d, 1H), 8.12 (d, 2H), 7.88 (t, 1H), 7.80 (d, 1H), 7.60 (t, 1H). MS (EI) for $C_{13}H_9N_3O$: 224 (MH^+).

[0151] 4-Chloro-2-pyridin-4-ylquinazoline: 2-Pyridin-4-ylquinazolin-4(3H)-one (1 mmol) and PCl_5 (1.5 mmol) were suspended in $POCl_3$ (12 mmol). The reaction mixture was brought to reflux over 4 h. The solvent was concentrated to dryness and the amorphous residue was partitioned with ethyl acetate and ice water. The aqueous layer was extracted with additional ethyl acetate and the combined organic layers were washed with 10% Na_2CO_3 and brine and dried over magnesium sulfate. The filtrate was concentrated and dried *in vacuo* to afford the desired product as a brown solid. (60% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.84 (d, 2H), 8.36 (d, 2H), 8.12 (m, 2H), 7.88 (m, 2H). MS (EI) for $C_{13}H_8ClN_3$: 242 (MH^+).

[0152] (1S,2R)-1-[(2-Pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: 4-Chloro-2-pyridin-4-ylquinazoline (1 mmol) was dissolved into N, N-dimethylacetamide (0.5 M), followed by addition of diispropylethylamine (2 mmol) and 1S, 2R-(-)-*cis*-1-amino-2-indanol (1.2 mmol) and was stirred at 85 °C for 2 h. The reaction was poured into water and back-extracted with ethyl acetate (3x). The combined organic layers were washed with 1N HCl, followed by a brine wash, and dried over magnesium sulfate. The final product was purified by MPLC and lyophilized to a yellow powder. (78%) ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.75 (d, 2H), 8.55 (d, 1H), 8.35 (m, 2H), 7.85 (d, 2H), 7.55 (m, 1H), 7.35 (d, 2H), 7.25 (m, 2H), 6.15 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355 (MH^+).

[0153] Using the same or similar synthetic techniques, substituting with the appropriate reagents such as the respective amines, the following compounds of the invention were prepared:

[0154] 2-Pyridin-4-yl-N-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.95 (d, 2H), 8.65 (d, 2H), 8.54 (d, 1H), 7.95 (m, 2H), 7.70

(m, 1H), 7.15 (m, 4H), 4.88 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 2H), 2.30 (m, 2H), 1.95 (m, 2H). MS (EI) for $C_{23}H_{20}N_4$: 353 (MH^+).

[0155] 2-Pyridin-4-yl-N-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine: ^1H NMR (400 MHz, d_6-DMSO): δ 8.76 (d, 2H), 8.44 (d, 1H), 8.35 (m, 2H), 7.85 (d, 2H), 7.58 (m, 1H), 7.15 (m, 4H), 4.80 (m, 1H), 3.30 (dd, 1H), 3.00 (d, 2H), 2.25 (m, 2H), 1.95 (m, 2H). MS (EI) for $C_{23}H_{20}N_4$: 353 (MH^+).

[0156] 4-[(1S)-2,3-Dihydro-1H-inden-1-ylmethyl]-2-pyridin-4-ylquinazoline: ^1H NMR (400 MHz, d_6-DMSO): δ 8.94 (d, 2H), 8.65 (d, 2H), 8.50 (d, 1H), 7.95 (m, 2H), 7.65 (m, 1H), 7.35 (m, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 6.34 (m, 1H), 3.12 (m, 1H), 2.99 (m, 1H), 2.66 (m, 1H), 2.22 (m, 1H). MS (EI) for $C_{22}H_{18}N_4$: 339 (MH^+).

[0157] (1R,2S)-1-[(2-Pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 8.95 (d, 2H), 8.65 (m, 3H), 7.95 (d, 2H), 7.65 (m, 1H), 7.35 (m, 2H), 7.25 (m, 2H), 6.15 (m, 1H), 4.78 (m, 1H), 3.25 (dd, 2H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355 (MH^+).

[0158] 1,1-Dimethylethyl-4-[(2-pyridin-4-ylquinazolin-4-yl)amino]piperidine-1-carboxylate: ^1H NMR (400 MHz, d_6-DMSO): δ 8.92 (m, 2H), 8.62 (m, 2H), 8.40 (d, 1H), 7.88 (m, 2H), 7.64 (m, 1H), 4.65 (m, 1H), 4.05 (m, 2H), 3.00 (m, 2H), 2.05 (d, 2H), 1.50, (m, 2H), 1.25 (br s, 9H). MS (EI) for $C_{23}H_{27}N_5O_2$: 406 (MH^+).

[0159] 1,1-Dimethylethyl-4-(2-pyridin-4-ylquinazolin-4-yl)piperazine-1-carboxylate: ^1H NMR (400 MHz, d_6-DMSO): δ 8.50 (d, 2H), 8.55 (d, 2H), 8.15 (m, 1H), 7.96 (m, 2H), 7.62 (m, 1H), 3.95 (m, 2H), 3.60 (m, 2H), 1.45 (br s, 9H). MS (EI) for $C_{22}H_{25}N_5O_2$: 392 (MH^+).

[0160] 2-Pyridin-4-yl-N-{[2,4,6-tris(methyloxy)phenyl]methyl}quinazolin-4-amine: ^1H NMR (400 MHz, d_6-DMSO): δ 9.00 (m, 2H), 8.60 (m, 2H), 8.50 (d, 1H), 7.96 (m, 2H), 7.60 (m, 1H), 6.30 (s, 1H), 6.25 (s, 2H), 4.8 (m, 1H). MS (EI) for $C_{20}H_{15}N_4O_3$: 403 (MH^+).

[0161] N-[(4-Fluorophenyl)methyl]-2-pyridin-4-ylquinazolin-4-amine: ^1H NMR (400 MHz, d_6-DMSO): δ 8.75 (d, 2H), 8.38 (d, 1H), 7.88 (m, 2H), 7.65 (m, 1H), 7.51 (m, 2H), 7.28 m, 2H), 7.24 (m, 3H), 4.94 (d, 1H), 4.28 (d, 1H). MS (EI) for $C_{23}H_{22}N_4F$: 331 (MH^+).

[0162] N-(2-Morpholin-4-ylethyl)-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.08 (d, 2H), 8.92 (d, 2H), 8.20 (d, 1H), 8.10 (m, 1H), 7.98 (t, 1H), 7.70 (t, 1H), 4.20 (br m, 2H), 3.35 (br m, 2H). MS (EI) for $C_{19}H_{21}N_5O$: 336 (MH^+).

[0163] 4-Piperazin-1-yl-2-pyridin-4-ylquinazoline: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.94 (d, 2H), 8.68 (d, 2H), 8.30 (m, 1H), 7.92 (m, 2H), 7.66 (m, 1H), 4.12 (m, 2H), 3.98 (m, 2H), 3.66 (br m, 4H), 3.54 (m, 2H), 3.22 (br m, 2H). MS (EI) for $C_{17}H_{17}N_5$: 292 (MH^+).

[0164] N-Piperidin-4-yl-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.05 (d, 2H), 8.85 (d, 2H), 8.65 (d, 1H), 8.09 (m, 1H), 7.98 (m, 1H), 7.72 (m, 1H), 4.75 (m, 1H), 3.40 (m, 2H), 3.15 (m, 2H), 2.15 (m, 2H), 2.08 (m, 2H). MS (EI) for $C_{18}H_{19}N_5$: 306 (MH^+).

[0165] 2-[(2-Pyridin-4-ylquinazolin-4-yl)amino]ethanol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.00 (m, 2H), 8.65 (m, 2H), 8.6 (m, 1H), 8.09 (m, 1H), 7.98 (m, 1H), 7.72 (m, 1H), 3.82 (m, 2H), 3.78 (m, 2H). MS (EI) for $C_{15}H_{14}N_4O$: 267 (MH^+).

[0166] N-(Cyclohexylmethyl)-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (m, 1H), 8.50 (d, 2H), 8.40 (d, 1H), 8.09 (m, 1H), 7.90 (m, 2H), 7.65 (m, 1H), 3.60 (m, 2H), 3.40 (m, 2H), 2.70 (br m, 5H), 1.20 (br m, 4H). MS (EI) for $C_{20}H_{22}N_4$: 319 (MH^+).

[0167] N-Cyclopentyl-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (m, 2H), 8.62 (m, 2H), 8.50 (d, 1H), 7.90 (m, 2H), 7.90 (m, 1H), 4.80 (m, 1H), 4.60 (m, 1H), 2.20 (m, 2H). MS (EI) for $C_{18}H_{18}N_4$: 291 (MH^+).

[0168] N-{(1S,2S)-2-[(Phenylmethyl)oxy]cyclopentyl}-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (m, 2H), 8.62 (m, 2H), 8.50 (d, 1H), 7.90 (m, 2H), 7.70 (m, 1H), 7.25 (m, 5H), 4.90 (m, 1H), 4.60 (m, 2H), 4.10 (m, 1H), 2.30 (m, 1H), 2.00 (m, 1H), 1.80 (m, 4H). MS (EI) for $C_{25}H_{24}N_4O$: 397 (MH^+).

[0169] N-Cyclohexyl-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (m, 2H), 8.60 (m, 2H), 8.50 (d, 1H), 7.90 (m, 2H), 7.90 (m, 1H), 4.80 (m, 1H), 4.40 (m, 1H), 2.10 (m, 2H), 1.80 (m, 2H), 1.70 (m, 2H), 1.60 (m, 3H), 1.20 (m, 1H). MS (EI) for $C_{19}H_{20}N_4$: 305 (MH^+).

[0170] N-Phenyl-N'-(2-pyridin-4-ylquinazolin-4-yl)benzene-1,4-diamine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.65 (d, 1H), 8.58 (d, 2H), 7.90 (m, 2H), 7.75 (m, 3H), 7.25 (br m, 4H), 7.15 (m, 2H), 6.85 (m, 1H). MS (EI) for $C_{25}H_{19}N_5$: 390 (MH^+).

[0171] N,N-Dimethyl-N'-(2-pyridin-4-ylquinazolin-4-yl)ethane-1,2-diamine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.62 (d, 2H), 8.40 (d, 1H), 7.96 (m, 2H), 7.70 (m, 1H), 4.20 (m, 2H), 3.50 (m, 2H), 2.90 (m, 6H). MS (EI) for $C_{17}H_{19}N_5$: 294 (MH^+).

[0172] 3-[(2-Pyridin-4-ylquinazolin-4-yl)amino]naphthalen-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.88 (d, 2H), 8.60 (m, 1H), 8.50 (m, 2H), 8.40 (m, 2H), 7.80 (br m, 4H), 7.4 (m, 2H). MS (EI) for $C_{23}H_{16}N_4O$: 365 (MH^+).

[0173] N-{4-[(1-Methylethyl)oxy]phenyl}-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.62 (d, 1H), 8.50 (d, 2H), 7.96 (m, 2H), 7.78 (m, 3H), 7.04 (d, 2H), 4.60 (m, 1H), 1.30 (m, 6H). MS (EI) for $C_{22}H_{20}N_4O$: 357 (MH^+).

[0174] 4-[4-(2-Pyridin-4-ylquinazolin-4-yl)piperazin-1-yl]phenol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.70 (d, 2H), 8.20 (d, 1H), 8.10 (m, 1H), 7.90 (m, 1H), 7.75 (m, 1H), 6.80 (m, 4H), 4.20 (br s, 4H), 3.50 (br s, 4H). MS (EI) for $C_{23}H_{21}N_5O$: 384 (MH^+).

[0175] (1S,2R)-1-[(2-Phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.80 (d, 1H), 8.40 (m, 2H), 8.05 (m, 2H), 7.70 (m, 3H), 7.35 (m, 4H), 6.25 (m, 1H), 4.80 (m, 1H), 3.25 (dd, 2H), 3.00 (d, 1H). MS (EI) for $C_{23}H_{19}N_3O$: 354 (MH^+).

[0176] (1R,2S)-1-[(2-Phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol:^{1}H NMR (400 MHz, d_6-DMSO): δ 8.80 (d, 1H), 8.40 (m, 2H), 8.05 (m, 2H), 7.70 (m, 3H), 7.30 (m, 4H), 6.25 (m, 1H), 4.80 (m, 1H), 3.25 (dd, 2H), 3.00 (d, 1H). MS (EI) for $C_{23}H_{19}N_3O$: 354 (MH^+).

[0177] (1R,2R)-2-[(2-Phenylquinazolin-4-yl)amino]cyclopentanol:^{1}H NMR (400 MHz, d_6-DMSO): δ 8.60 (d, 1H), 8.40 (m, 2H), 8.00 (m, 2H), 7.70 (m, 4H), 4.50 (m, 1H), 4.30 (m, 1H), 2.25 (m, 1H), 1.99 (m, 1H), 1.70 (br m, 4H), 1.60 (m, 1H). MS (EI) for $C_{19}H_{19}N_3O$: 306 (MH^+).

[0178] (1R,2R)-2-[(2-Phenylquinazolin-4-yl)amino]cyclohexanol:^{1}H NMR (400 MHz, d_6-DMSO): δ 8.55 (d, 1H), 8.40 (m, 2H), 8.00 (m, 2H), 7.70 (m, 4H), 4.50 (m, 1H), 3.70 (m, 1H), 2.00 (m, 2H), 1.70 (m, 2H), 1.20 (br m, 4H). MS (EI) for $C_{20}H_{21}N_3O$: 320 (MH^+).

[0179] (1S,2R,3R,5R)-3-(Hydroxymethyl)-5-[(2-phenylquinazolin-4-yl)amino]cyclopentane-1,2-diol:^{1}H NMR (400 MHz, d_6-DMSO): δ 8.60 (d, 1H), 8.40 (d, 2H), 8.00 (m, 2H), 7.70 (m, 4H), 4.90 (m, 1H), 4.00 (m, 1H), 3.80 (m, 1H), 2.35 (m, 1H), 2.00 (m, 1H), 1.40 (m, 1H). MS (EI) for $C_{20}H_{21}N_3O_3$: 352 (MH^+).

[0180] (1S,2R)-1-[(2-Pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.70 (d, 1H), 8.00 (m, 2H), 7:80 (m, 1H), 7.70 (m, 1H), 7.35 (m, 4H), 6.2 (m, 1H), 4.80 (m, 1H), 3.25 (dd, 2H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355 (MH^+).

[0181] (1R,2S)-1-[(2-Pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.90 (d, 2H), 8.70 (d, 1H), 7.98 (m, 2H), 7.80 (m, 1H), 7.70 (m, 1H), 7.35 (m, 4H), 6.2 (m, 1H), 4.80 (m, 1H), 3.25 (dd, 2H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355 (MH^+).

[0182] (1R,2R)-2-[(2-Pyridin-3-ylquinazolin-4-yl)amino]cyclopentanol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.60 (S, 1H), 8.90 (d, 1H), 8.80 (d, 1H), 8.00 (m, 4H), 7.75 (m, 4H), 4.70 (m, 1H), 4.25 (m, 1H), 2.25 (m, 1H), 1.99 (m, 1H), 1.70 (br m, 4H), 1.60 (m, 1H). MS (EI) for $C_{18}H_{18}N_4O$: 307 (MH^+).

[0183] (1R,2R)-2-[(2-Pyridin-3-ylquinazolin-4-yl)amino]cyclohexanol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.50 (m; 1H), 8.90 (m, 1H), 8.78 (d, 1H), 8.55 (d, 1H), 8.00 (m, 2H), 7.80 (m, 2H), 7.70 (m, 4H), 4.40 (m, 1H), 3.65 (m, 1H), 2.00 (m, 2H), 1.70 (m, 2H), 1.40 (br m, 4H). MS (EI) for $C_{19}H_{20}N_4O$: 321(MH^+).

[0184] (1S,2R)-1-[(2-Pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.95 (d, 1H), 8.85 (d, 1H), 8.80 (m, 1H), 8.30 (d, 1H), 8.20 (t, 1H), 8.10 (t, 1H), 7.90 (m, 1H), 7.80 (m, 1H), 7.30 (m, 4H), 6.35 (m, 1H), 4.80 (m, 1H), 3.30 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355(MH^+).

[0185] (1R,2S)-1-[(2-Pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.95 (d, 1H), 8.85 (d, 1H), 8.80 (m, 1H), 8.30 (d, 1H), 8.20

(t, 1H), 8.10 (t, 1H), 7.90 (m, 1H), 7.80 (m, 1H), 7.30 (m, 4H), 6.35 (m, 1H), 4.80 (m, 1H), 3.30 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{18}N_4O$: 355(MH^+).

[0186] (2R)-3-Phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 9.00 (m, 2H), 8.70 (m, 1H), 8.55 (m, 1H), 8.40 (m 1H), 7.90 (m, 2H), 7.70 (m, 1H), 7.40-7.00 (m, 5H), 4.80 (m, 1H), 3.70 (m, 2H), 3.10 (m, 1H), 3.00 (m, 1H). MS (EI) for $C_{22}H_{20}N_4O$: 357(MH^+).

[0187] (2S)-3-Phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 9.00 (m, 2H), 8.60 (m, 1H), 8.49 (d, 1H), 7.90 (m, 2H), 7.70 (m, 1H), 7.40-7.07 (m, 5H), 4.90 (m, 1H), 3.70 (m, 2H), 3.11 (m, 1H), 3.00 (m, 1H). MS (EI) for $C_{22}H_{20}N_4O$: 357(MH^+).

[0188] 2-[(Phenylmethyl)(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol: ^1H NMR (400 MHz, d_6-DMSO): δ 8.94 (d, 2H), 8.56 (d, 2H), 8.24 (d, 1H), 7.96 (m, 1H), 7.88 (m, 1H), 7.58-7.28 (br m, 6H), 5.25 (br s, 2H), 3.95 (br s, 4H). MS (EI) for $C_{22}H_{20}N_4O$: 357(MH^+).

[0189] 6-Chloro-2-pyridin-4-ylquinazolin-4-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.80 (d, 2H), 8.20 (d, 1H), 8.12 (b, 2H), 7.80 (d, 1H), 7.40 (d, 1H). MS (EI) for $C_{13}H_8N_3OCl$: 258 (MH^+).

[0190] 4,6-Dichloro-2-pyridin-4-ylquinazoline: ^1H NMR (400 MHz, d_4-Methanol): δ 8.9 (d, 2H), 8.8 (d, 2H), 8.4 (s, 1H), 8.2 (d of d, 2H). MS (EI) for $C_{13}H_7Cl_2N_3$: 276 (MH^+).

[0191] (1S,2R)-1-[(6-Chloro-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 9.0, (d, 2H), 8.55 (d, 1H), 7.8 (m, 2H), 7.25 (m, 2H), 7.35 (m, 2H), 7.25 (m, 2H), 6.15 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{17}N_4OCl$: 389 (MH^+).

[0192] 6,7-Bis(methyloxy)-2-pyridin-4-ylquinazolin-4-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.80 (d, 2H), 8.50 (m, 2H), 7.60 (1H), 7.25 (1H), 4.0 (s,3H), 4.1(s,3H), . MS (EI) for $C_{15}H_{13}N_3O3$: 284 (MH^+).

[0193] 4-Chloro-6,7-bis(methyloxy)-2-pyridin-4-ylquinazoline: ^1H NMR (400 MHz, d_4-Methanol): δ 8.9 (m, 4H), 7.60 (1H), 7.25 (1H), 4.0 (s,3H), 4.1(s,3H),. MS (EI) for $C_{15}H_{12}ClN_3O_2$: 302 (MH^+).

[0194] (1S,2R)-1-{[6,7-Bis(methyloxy)-2-pyridin-4-ylquinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.9.0, (d, 2H), 8.6 (d, 2H), 7.8 (s 1H), 7.4 (s, 1H),7.25 (m, 2H), 7.35 (m, 2H), 6.15 (d, 1H), 4.0 (s,3H), 4.1(s,3H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{24}H_{22}N_4O_3$: 415 (MH^+).

[0195] 6-Bromo-2-pyridin-4-ylquinazolin-4-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.80 (d, 2H), 8.40 (d, 2H), 8.25 (s, 1H), 7.80 (d, 1H), 8.0 (d, 1H). MS (EI) for $C_{13}H_8N_3OBr$: 302/304 (MH^+).

[0196] 6-Bromo-4-chloro-2-pyridin-4-ylquinazoline: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.9 (m, 4H), 8.4 (s, 1H), 8.1 (d 1H), 8.2 (d 1H). MS (EI) for $C_{13}H_7BrClN_3$: 320/322 (MH^+).

[0197] (1S,2R)-1-[(6-Bromo-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.0, (m, 4H), 8.7 (d, 1H), 8.1 (d 1H), 7.9 (d 1H), 7.35 (m, 2H), 7.25 (m, 2H), 6.15 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{22}H_{17}N_4OBr$: 434 (MH^+).

[0198] 7-Methyl-2-pyridin-4-ylquinazolin-4-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.90 (m, 2H), 8.15 (d, 1H), 8.2 (m, 2H), 7.70 (s, 1H), 7.45 (d, 1H), 2.6 (s, 3H). MS (EI) for $C_{14}H_{11}N_3O$: 238 (MH^+).

[0199] 4-Chloro-7-methyl-2-pyridin-4-ylquinazoline: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.9 (m, 4H), 8.25 (d, 1H), 8.0 (s,1H), 7.8 (d, 1H) 2.6 (s, 3H). MS (EI) for $C_{14}H_{10}ClN_3$: 256 (MH^+).

[0200] (1S,2R)-1-[(7-Methyl-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.0, (d, 2H), 8.4 (d, 1H), 8.7 (d, 2H), 7.8 (d, 1H), 7.6 (d, 1H), 7.25 (m, 4H), 6.15 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H) 2.6 (s, 3H). MS (EI) for $C_{23}H_{20}N_4O$: 369 (MH^+).

[0201] 2-Pyrazin-2-ylquinazolin-4-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.30, (br s, 1H), 9.58 (s, 1H), 8.92-8.88 (m, 2 H), 8.24-8.18 (m, 1H), 7.94-7.82 (m, 2H), 7.65-7.58 (m, 1H). MS (EI) for $C_{12}H_8N_4O$: 225 (MH^+).

[0202] (1S,2R)-1-[(2-Pyrazin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.85 (s, 1H), 8.98-8.94 (m, 2H), 8.62-8.58 (m, 1H), 8.19-

8.08 (m, 2H), 7.85-7.79 (m, 1H), 7.45-7.25 (m, 4H), 6.44-6.41 (m, 1H), 4.99-4.94 (m, 1H), 3.44-3.36 (m, 1H), 3.17-3.11 (m, 1H). MS (EI) for $C_{21}H_{17}N_5O$: 356 (MH^+).

[0203] (1S,2R)-1-(Quinazolin-4-ylamino)-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 10.10 (br s, 1H), 8.96 (s, 1H), 8.81-8.78 (m, 1H), 8.07-8.00 (m, 1H), 7.84-7.72 (m, 2H), 7.35-7.20 (m, 4H), 6.06-6.01 (m, 1H), 5.32 (br s, 1 H), 4.74-4.68 (m, 1H), 3.25-3.14 (m, 1H), 3.01-2.93 (m, 1H). MS (EI) for $C_{17}H_{15}N_3O$: 278 (MH^+).

[0204] (1R,2S)-1-(Quinazolin-4-ylamino)-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.82 (s, 1H), 8.55-8.52 (m, 1H), 8.08-8.04 (m, 1H), 7.82-7.76 (m, 2H), 7.37-7.24 (m, 4H), 6.23-6.22 (m, 1H), 4.87-4.83 (m, 1H), 3.34-3.28 (m, 1H), 3.13-3.08 (m, 1H). MS (EI) for $C_{17}H_{15}N_3O$: 278 (MH^+).

[0205] (1S,2R)-1-{[2-(2-Ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.82-8.70 (m, 3H), 8.44-8.41 (m, 1H), 8.02-7.99 (m, 2H), 7.76-7.72 (m, 1H), 7.38-7.22 (m, 4H), 6.31-6.28 (m, 1H), 4.90-4.87 (m, 1H), 3.38-3.32 (m, 1H), 3.19-3.08 (m, 3H), 1.50-1.45 (m, 3H). MS (EI) for $C_{24}H_{22}N_4O$: 383 (MH^+).

[0206] (1R,2S)-1-{[2-(2-Ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.82-8.70 (m, 3H), 8.43-8.39 (m, 1H), 8.03-7.96 (m, 2H), 7.75-7.70 (m, 1H), 7.39-7.21 (m, 4H), 6.30-6.27 (m, 1H), 4.91-4.87 (m, 1H), 3.39-3.31 (m, 1H), 3.19-3.08 (m, 3H), 1.50-1.44 (m, 3H). MS (EI) for $C_{24}H_{22}N_4O$: 383 (MH^+).

[0207] 2-(2-Ethylpyridin-4-yl)quinazolin-4-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.75-8.72 (m, 1H), 8.25-8.21 (m, 1H), 8.14-8.10 (m, 1H), 7.74-7.64 (m, 2H), 7.45-7.40 (m, 1H), 6.87-6.83 (m, 1H), 3.91 (s, 3H). MS (EI) for $C_{14}H_{11}N_3O_2$: 254 (MH^+).

[0208] (1S,2R)-1-{[2-[6-(Methyloxy)pyridin-3-yl]-7-(trifluoromethyl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 9.20-9.18 (m, 1H), 8.63-8.52 (m, 2H), 8.09-8.04 (m, 1H), 7.97-7.93 (m, 1H), 7.79-7.74 (m, 1H), 7.42-7.24 (m, 4H), 7.08-7.04 (m, 1H), 6.34-6.31 (m, 1H), 4.94-4.89 (m, 1H), 4.06 (s, 3H), 3.40-3.33 (m, 1H), 3.15-3.09 (m, 1H). MS (EI) for $C_{23}H_{20}N_4O_2$: 385 (MH^+).

[0209] (1S,2R)-1-({2-[2,4-Bis(methyloxy)pyrimidin-5-yl]-quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 9.18 (s, 1H), 8.53-8.50 (m, 1H), 8.08-7.95 (m, 2H), 7.78-7.72 (m, 1H), 7.38-7.24 (m, 4H), 6.41-6.38 (m, 1H), 4.90-4.85

(m, 1H), 4.22 (s, 3H), 3.66 (s, 3H), 3.39-3.32 (m, 1H), 3.14-3.08 (m, 1H). MS (EI) for $C_{23}H_{21}N_5O_3$: 416 (MH^+).

[0210] (1S,2R)-1-{[2-(1-Methyl-1H-imidazol-2-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 8.36-8.32 (m, 1H), 7.99-7.90 (m, 2H), 7.71-7.60 (m, 3H), 7.36-7.22 (m, 4H), 6.23-6.20 (m, 1H), 4.85-4.81 (m, 1H), 4.45 (s, 3H), 3.35-3.31 (m, 1H), 3.11-3.05 (m,1 H). MS (EI) for $C_{21}H_{19}N_5O$: 358 (MH^+).

[0211] (1S,2R)-1-{[2-(4-Aminopyridin-3-yl)-quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: ^1H NMR (400 MHz, d_4-Methanol): δ 9.28 (s, 1H), 8.33-8.31 (m, 1H), 8.08-8.04 (m, 1H), 7.92-7.90 (m, 2H), 7.66-7.60 (m, 1H), 7.38-7.20 (m, 4H), 7.09-7.06 (m, 1H), 6.12-6.08 (m, 1H), 4.86-4.81 (m, 1H), 3.35-3.31 (m, 1H), 3.12-3.05 (m, 1H). MS (EI) for $C_{22}H_{19}N_5O$: 370 (MH^+).

[0212] (2R)-2-Phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol: ^1H NMR (400 MHz, d_6-DMSO): δ 8.95 (m 2H), 8.65 (m 1H), 8.59 (m 2H), 7.95 (m 2H), 7.75 (m 2H), 7.6 (m 2H), 7.4 (m 2H), 7.2 (m 1H), 5.65 (m 1H), 4.0 (m 1H), 3.8 (m 1H). MS (EI) for $C_{21}H_{18}N_4O$: 343 (MH^+).

[0213] (2S)-2-Phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol: ^1H NMR (400 MHz, d_6-DMSO): δ 8.95 (m 2H), 8.65 (m 1H), 8.59 (m 2H), 7.95 (m 2H), 7.75 (m 2H), 7.6 (m 2H), 7.4 (m 2H), 7.2 (m 1H), 5.65 (m 1H), 4.0 (m 1H), 3.8 (m 1H). MS (EI) for $C_{21}H_{18}N_4O$: 343 (MH^+).

[0214] (2S)-3-Methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 9.00 (m 2H), 8.60 (m 3H), 7.95 (m 2H), 7.75 (m 1H), 4.6 (m 1H), 3.75 (m 2H), 2.2 (m 1H), 1.0 (m 6H). MS (EI) for $C_{18}H_{20}N_4O$: 309 (MH^+).

[0215] (2R)-3-Methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 9.00 (m 2H), 8.60 (m 3H), 7.95 (m 2H), 7.75 (m 1H), 4.6 (m 1H), 3.75 (m 2H), 2.2 (m 1H), 1.0 (m 6H). MS (EI) for $C_{18}H_{20}N_4O$: 309 (MH^+).

[0216] 2-Pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)quinazolin-4-amine: ^1H NMR (400 MHz, d_6-DMSO): δ8.95 (m 4H), 8.20 (m 1H), 8.0 (m 2H), 7.70 (m 1H), 4.20 (m 2H), 3.8 (m 2H), 3.70 (m 2H), 3.20 (m 2H), 2.20-2.00 (m 4H). MS (EI) for $C_{19}H_{21}N_5$: 320 (MH^+).

[0217] 1-(2-Pyridin-4-ylquinazolin-4-yl)piperidin-3-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.00 (m 1H), 8.70 (m 1H), 8.5 (m 1H), 8.3 (m 1H), 8.0 (m 2H), 7.65 (m 2H), 4.4 (m 1H), 4.0 (m 4H), 2.1 (m 2H), 1.9 (m 2H). MS (EI) for $C_{18}H_{18}N_4O$: 307 (MH^+).

[0218] N-Piperidin-1-yl-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.85 (m 2H), 8.35 (m 3H), 7.85-7.60 (m 3H), 2.20 (m 4H), 1.70 (m 6H). MS (EI) for $C_{18}H_{19}N_5$: 306 (MH^+).

[0219] 3-[(2-Pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.95 (d, 2H), 8.60 (d, 2H), 8.40 (d, 1H), 7.9 (d, 2H), 7.7 (m, 1H), 3.8 (m, 2H), 3.5 (m, 2H), 1.9 (m, 2). MS (EI) for $C_{16}H_{16}N_4O$: 281 (MH^+).

[0220] N-[(3S)-Piperidin-3-yl]-2-pyridin-4-ylquinazolin-4-amine:^{1}H NMR (400 MHz, d_4-Methanol): δ 9.00 (m 4H), 8.20 (m 1H), 8.1 (m 1H), 7.95 (m 1H), 7.7 (m 1H), 4.6 (m 1H), 4.25 (m 1H), 3.65 (m 3H), 2.25 (m 1H), 2.1 (m 1H), 1.95 (m 2H). MS (EI) for $C_{18}H_{19}N_5$: 306 (MH^+).

[0221] (2S)-1-[(2-Pyridin-4-ylquinazolin-4-yl)amino]propan-2-ol:^{1}H NMR (400 MHz, d_6-DMSO): δ 9.00 (m 2H), 8.50 (m 1H), 8.0 (m 3H), 7.7 (m 1H), 4.1 (m 1H), 1.2 (m 2H), 1.1 (m 3H). MS (EI) for $C_{16}H_{16}N_4O$: 281 (MH^+).

[0222] (2S)-3-[(2-Pyridin-4-ylquinazolin-4-yl)amino]propane-1,2-diol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.95 (m 2H), 8.85 (m 2H), 8.30 (m 1H), 8.00 (m 2H), 7.85 (m 1H), 4.10 (m 2H), 3.95 (m 1H), 3.65 (m 2H). MS (EI) for $C_{16}H_{16}N_4O_2$: 297 (MH^+).

[0223] [(2S)-1-(2-Pyridin-4-ylquinazolin-4-yl)-2,3-dihydro-1H-indol-2-yl]methanol: ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.0 (m 2H), 8.2-8.0 (m 3H), 7.7 (m 1H), 7.4-7.1 (m 4H), 5.1-5.0 (m 2H), 3.6-3.3 (m 3H). MS (EI) for $C_{22}H_{18}N_4O$: 355 (MH^+).

[0224] (2R)-2-[(2-Pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol: ^{1}H NMR (400 MHz, d_4-Methanol): δ8.95 (m 2H), 8.65 (m 2H), 8.40 (m 1H), 8.00 (m 2H), 7.75 (m 1H), 4.95 (m 2H), 3.85 (m 1H), 1.40 (m 3H). MS (EI) for $C_{16}H_{16}N_4O$: 281 (MH^+).

[0225] N-(2-Piperazin-1-ylethyl)-2-pyridin-4-ylquinazolin-4-amine:^{1}H NMR (400 MHz, d_4-Methanol): δ 8.95 (m 2H), 8.85 (m 2H), 8.30 (m 1H), 8.00 (m 2H), 7.85 (m 1H), 4.10 (m 2H), 3.4-2.8 (m 10H). MS (EI) for $C_{19}H_{22}N_6$: 335 (MH^+).

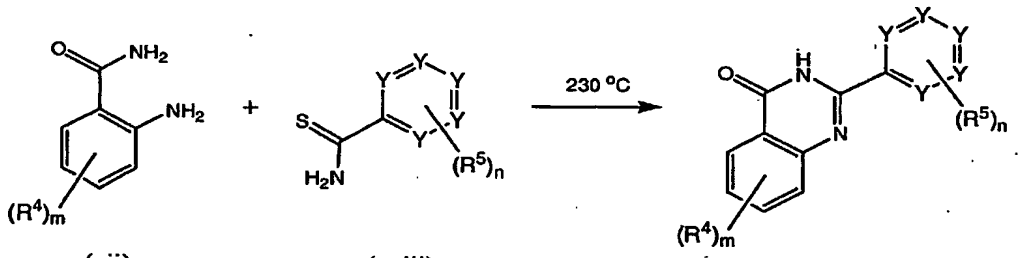
[0226] 2-{4-[(2-Pyridin-4-ylquinazolin-4-yl)amino]piperazin-1-yl}ethanol: ^{1}H NMR (400 MHz, d_4-Methanol): δ8.95 (m 2H), 8.30 (m 2H), 8.00-7.65 (m 4H), 3.90 (m 4H), 3.75 (m 2H), 3.60 (m 2H), 3.35 (m 4H). MS (EI) for $C_{19}H_{22}N_6O$: 351 (MH^+).

[0227] N-(2,3-Dihydro-1H-inden-1-yl)-2-pyridin-4-ylquinazolin-4-amine: ^{1}H NMR (400 MHz, d_4-Methanol): δ8.95 (m 2H), 8.70 (m 2H), 8.40 (m 1H), 8.00 (m 2H), 7.75 (m 1H), 7.45-7.20 (m 4H), 6.4 (m 1H), 3.2-3.0 (m 2H), 2.80 (m 1H), 2.25 (m 1H). MS (EI) for $C_{22}H_{18}N_4$: 339 (MH^+).

Example 2

[0228] Scheme 8 shows that intermediate (xiv) can be made via thioamide (xviii) as an alternative to using aldehyde intermediate (xiii) as outlined in Scheme 6 above.

Scheme 8



(xii) (xviii) (xiv)

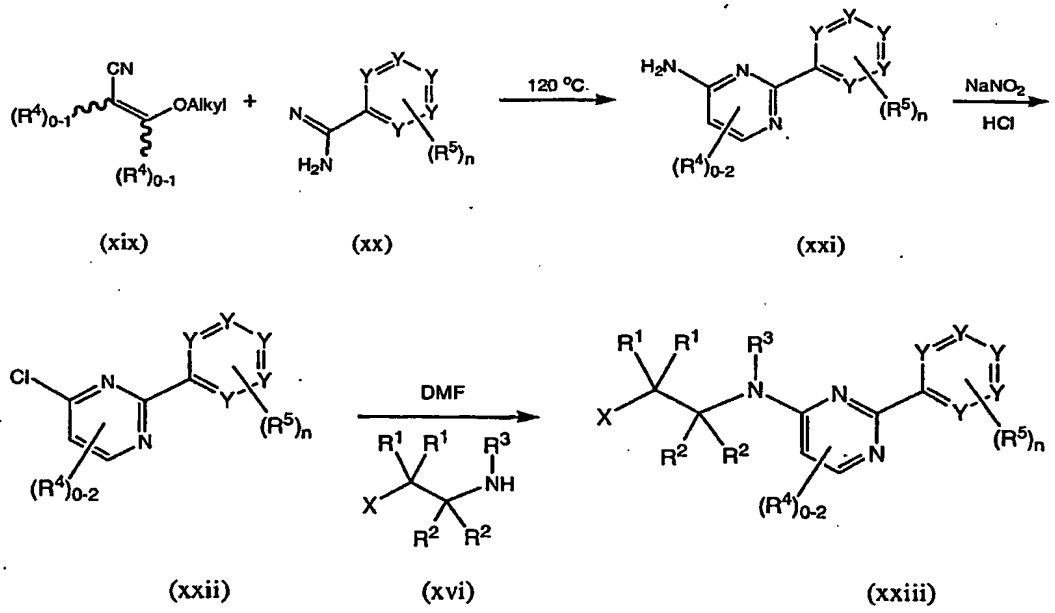
[0229] 2-Pyridin-4-yl-7-(trifluoromethyl)quinazolin-4-amine: Isothionicotinamide (1 mmol) and 2-amino-4-trifluoromethylbenzoic acid (1 mmol) were fused in a pressure tube under nitrogen atmosphere for 15 min. Upon cooling, the material was extracted with methanol and concentrated on a rotary evaporator. The residue was suspended in $POCl_3$ (12 mmol) and PCl_5 (1.5 mmol) was added. The reaction mixture was brought to reflux over 4 h. The solvent was concentrated to dryness and the amorphous residue was partitioned with ethyl acetate and ice water. The aqueous layer was extracted with additional ethyl acetate and the combined organic layers were washed with 10% Na_2CO_3 and brine and dried over magnesium sulfate. The filtrate was concentrated and dried *in vacuo* to afford the desired product as a brown solid. (60% yield). ^{1}H NMR (400 MHz, d_4-Methanol): δ 8.9 (m, 4H), 8.4 (m, 2H), 8.2 (m, 1H). MS (EI) for $C_{14}H_7ClF_3N_3$: 310 (MH^+).

[0230] (1S,2R)-1-{[2-Pyridin-4-yl-7-(trifluoromethyl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol: This compound was prepared using the method described above for the addition of amine to 4-chloroquinazoline. ^{1}H NMR (400 MHz, d_4-Methanol): δ 9.0, (d, 2H), 8.55 (d, 1H), 8.9 (m, 2H), 8.25 (m, 1H), 7.85 (m, 1H), 7.25 (m, 4H), 6.15 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{23}H_{17}N_4OF_3$: 423 (MH^+).

Example 3

[0231] Scheme 9 shows how compounds, (xxiii), of the invention are made via 4-chloropyrimidine, (xxii), analogous to 4-chloroquinazoline intermediate (xv) above. Starting acrylonitrile (xix) is reacted with aryl amidine (xx) to give 4-aminopyrimidine (xxi). Sandmeyer reaction of (xxi) gives 4-chloropyrimidine (xxii), which is then reacted with amine (xvi) to give compounds (xxiii).

Scheme 9



[0232] (1S,2R)-1-[(2-Pyridin-4-ylpyrimidin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol: A mixture of 4-pyridinecarboxamidine (1 mmol) and 3-ethoxyacrylonitrile (1 mmol) was

heated to 120 °C in the absence of solvent for 3 h. The mixture was cooled to room temperature and extracted with methanol. The methanol was removed on a rotary evaporator and the residue was taken up in ice cold concentrated HCl (10 mL). The solution was cooled to 0 °C and sodium nitrite (2.5 mmol) in water (5 mL) was added dropwise such that the temperature was maintained below 10 °C. The reaction was stirred for 30 min, then poured over ice and made basic (pH > 8) by the addition of 3 N sodium hydroxide. The mixture was then extracted with ethyl acetate and the combined organic layers were washed with 10% Na_2CO_3 and brine and dried over magnesium sulfate. The filtrate was concentrated and dried *in vacuo* to afford the chloropyrimidine. This material was dissolved into N, N-dimethylacetamide (0.5 M), followed by addition of diispropylethylamine (2 mmol) and 1S, 2R-(-)-*cis*-1-amino-2-indanol (1.2 mmol) and was stirred at 85 °C for 2 h. The reaction was poured into water and back-extracted with ethyl acetate (3x). The combined organic layers were washed with 1N HCl, followed by a brine wash, and dried over magnesium sulfate. The final product was purified by MPLC and lyophilized. ^1H NMR (400 MHz, d_4-Methanol): δ 9.0, (d, 2H), 8.25 (d, 1H), 8.6 (d, 2H), 7.0 (d, 1H), 7.25 (m, 4H), 6.0 (m, 1H), 4.85 (m, 1H), 3.25 (dd, 1H), 3.00 (d, 1H). MS (EI) for $C_{18}H_{16}N_4O$: 305 (MH^+).

Assays

[0233] For assay of activity, generally Tie-2, or a compound according to the invention is non-diffusably bound to an insoluble support having isolated sample-receiving areas (e.g., a microtiter plate, an array, etc.). The insoluble support may be made of any composition to which the compositions can be bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharides, nylon or nitrocellulose, Teflon™, etc. Microtiter plates and arrays are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. The particular manner of binding of the composition is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the composition and is nondiffusable. Exemplary methods of binding include the use of antibodies (which do not

sterically block either the ligand binding site or activation sequence when the protein is bound to the support), direct binding to "sticky" or ionic supports, chemical crosslinking, the synthesis of the protein or agent on the surface, etc. Following binding of the protein or agent, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

[0234] One measure of inhibition is K_i. For compounds with IC_{50}'s less than 1 μM, the K_i or K_d is defined as the dissociation rate constant for the interaction of the agent with a Tie-2. Exemplary compositions have K_i's of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having K_i's of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound is determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is

$$V = V_{max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

zero. The rate (i.e., compound concentration) data are fitted to the equation:

[0235] Where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

[0236] Another measure of inhibition is GI_{50}, defined as the concentration of the compound that results in a decrease in the rate of cell growth by fifty percent. Exemplary compounds have GI_{50}'s of, for example, less than about 1 mM, less than about 10 μM, less than about 1 μM, and further, for example, having GI_{50}'s of less than about 100 nM, still further having GI_{50}'s of less than about 10 nM. Measurement of GI_{50} is done using a cell proliferation assay.

[0237] Tyrosine kinase activity is determined by 1) measurement of kinase-dependent ATP consumption by in the presence of a generic substrate such as polyglutamine, tyrosine (pEY),

by luciferase/luciferin-mediated chemiluminescence or; 2) incorporation of radioactive phosphate derived from ^{33}P-ATP into a generic substrate which has been adsorbed onto the well surface of polystyrene microtiter plates. Phosphorylated substrate products are quantified by scintillation spectrometry.

Structure Activity Relationships

[0238] Table 2 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than or equal to 1000 nM, C = IC_{50} greater than 1000 nM, but less than 10,000 nM, and D = IC_{50} 10,000 nM or greater. The abbreviation for human enzyme, Tie-2, is defined as tyrosine kinase with immunoglobulin and EGF repeats.

Table 2

#	Name	Tie-2 IC_{50}
1	N-cyclohexyl-2-pyridin-4-ylquinazolin-4-amine	C
2	2-pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)quinazolin-4-amine	D
3	N-cyclopentyl-2-pyridin-4-ylquinazolin-4-amine	C
4	N-(cyclohexylmethyl)-2-pyridin-4-ylquinazolin-4-amine	C
5	2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol	D
6	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol	D
7	N-[(4-fluorophenyl)methyl]-2-pyridin-4-ylquinazolin-4-amine	C
8	N,N-dimethyl-N'-(2-pyridin-4-ylquinazolin-4-yl)ethane-1,2-diamine	D
9	N-(2,3-dihydro-1H-inden-1-yl)-2-pyridin-4-ylquinazolin-4-amine	B
10	N-(2-morpholin-4-ylethyl)-2-pyridin-4-ylquinazolin-4-amine	D
11	4-[4-(2-pyridin-4-ylquinazolin-4-yl)piperazin-1-yl]phenol	D
12	2-pyridin-4-yl-N-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine	B

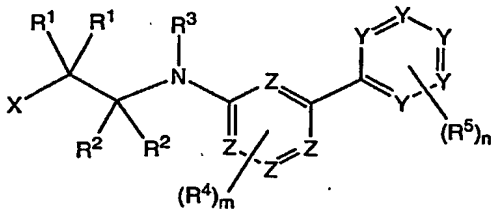
#	Name	Tie-2 IC_{50}
13	4-piperazin-1-yl-2-pyridin-4-ylquinazoline	D
14	1,1-dimethylethyl 4-(2-pyridin-4-ylquinazolin-4-yl)piperazine-1-carboxylate	D
15	2-pyridin-4-yl-N-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine	C
16	4-[(1S)-2,3-dihydro-1H-inden-1-ylmethyl]-2-pyridin-4-ylquinazoline	C
17	(1R,2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
18	(1S,2R)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	A
19	1,1-dimethylethyl 4-[(2-pyridin-4-ylquinazolin-4-yl)amino]piperidine-1-carboxylate	C
20	2-pyridin-4-yl-N-{[2,4,6-tris(methyloxy)phenyl]methyl}quinazolin-4-amine	D
21	N-piperidin-4-yl-2-pyridin-4-ylquinazolin-4-amine	D
22	N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}-2-pyridin-4-ylquinazolin-4-amine	D
23	N-phenyl-N'-(2-pyridin-4-ylquinazolin-4-yl)benzene-1,4-diamine	D
24	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]naphthalen-2-ol	C
25	N-{4-[(1-methylethyl)oxy]phenyl}-2-pyridin-4-ylquinazolin-4-amine	C
26	(1S,2R)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
27	(1R,2S)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
28	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclopentanol	D
29	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclohexanol	D
30	(1S,2R,3R,5R)-3-(hydroxymethyl)-5-[(2-phenylquinazolin-4-yl)amino]cyclopentane-1,2-diol	D
31	(1S,2R)-1-[(6-chloro-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	A
32	N-(2-piperazin-1-ylethyl)-2-pyridin-4-ylquinazolin-4-amine	D
33	(1S,2R)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	C

#	Name	Tie-2 IC_{50}
34	(1R,2S)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
35	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclopentanol	D
36	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclohexanol	D
37	(1S,2R)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
38	(1R,2S)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
39	(2S)-3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propane-1,2-diol	D
40	[(2S)-1-(2-pyridin-4-ylquinazolin-4-yl)-2,3-dihydro-1H-indol-2-yl]methanol	D
41	(2R)-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol	D
42	(2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-2-ol	D
43	(1S,2R)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	D
44	(1R,2S)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	D
45	(1S,2R)-1-[(6-bromo-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	A
46	(1S,2R)-1-{[6,7-bis(methyloxy)-2-pyridin-4-ylquinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	B
47	1-(2-pyridin-4-ylquinazolin-4-yl)piperidin-3-ol	D
48	(1S,2R)-1-{[2-pyridin-4-yl-7-(trifluoromethyl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	B
49	(1S,2R)-1-({2-[6-(methyloxy)pyridin-3-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol	C
50	N-[(3S)-piperidin-3-yl]-2-pyridin-4-ylquinazolin-4-amine	D
51	(1S,2R)-1-[(7-methyl-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	A
52	(1S,2R)-1-({2-[2,4-bis(methyloxy)pyrimidin-5-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol	D
53	(2R)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol	D
54	(2S)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol	C

#	Name	Tie-2 IC_{50}
55	(2S)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol	C
56	(2R)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol	C
57	(1S,2R)-1-[(2-pyridin-4-ylpyrimidin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	B
58	(1S,2R)-1-[(2-pyrazin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol	D
59	(1S,2R)-1-{[2-(4-aminopyridin-3-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	D
60	(2R)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol	D
61	(2S)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol	C
62	2-[(phenylmethyl)(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol	C
63	(1S,2R)-1-{[2-(2-aminopyrimidin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol	B
64	5-(4-{[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}quinazolin-2-yl)pyridin-2-ol	D
65	(1S,2R)-1-({2-[2-(methylthio)pyrimidin-4-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol	D

What is claimed is:

1. A compound for modulating kinase activity, particularly Tie-2, of Formula I,

I 

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

X is selected from -H, $-OR^6$, $-SR^6$, $-N(R^6)R^7$, absent, oxo, thiono, and imino, with the proviso that when X is oxo, thiono, or imino, there is only one R^1;

R^1 and R^2 are each independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and absent;

optionally two of R^2 together are oxo;

optionally, at least one pair of substituents, selected from two of R^1, two of R^2, and one each of R^1 and R^2, together with the corresponding carbon or carbons to which they are attached, form a first ring system comprising between 3 and 7 ring atoms, said first ring system optionally substituted with between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the first ring system to which they are attached, form a second ring system comprising between 3 and 7 ring atoms, said second ring system optionally substituted with between 0 and 3 of R^1;

R^3 is selected from -H, optionally substituted lower alkyl, optionally substituted lower arylalkyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted alkoxy; or

R^3 and one of R^2, together with the atoms to which each is attached, form a third ring system comprising between 3 and 7 ring atoms, said third ring system optionally substituted with

between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the third ring system to which they are attached, form a fourth ring system comprising between 3 and 7 ring atoms, said fourth ring system optionally substituted with between 0 and 3 of R^1; or

R^3 and one of R^1, together with the atoms to which they are attached and the carbon to which R^2 is attached, form a fifth ring system comprising between 3 and 7 ring atoms atoms, said fifth ring system optionally substituted with between 0 and 4 additional of R^1, each independently selected as defined above and optionally, when paired, together with the corresponding atom or atoms of the fifth ring system to which they are attached, form a sixth ring system comprising between 3 and 7 ring atoms, said sixth ring system optionally substituted with between 0 and 3 of R^1;

m is 0 to 4;

R^4 is independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl;

optionally two adjacent R^4's, together with the two carbons to which they are attached, form a seventh ring system fused with the aromatic ring system to which said two adjacent R^4's are attached as in formula I, said seventh ring system comprising between 5 and 7 atoms and substituted with 0 to 3 additional of R^4, provided said seventh ring system fused with the aromatic ring system to which said two adjacent R^4's are attached, does not constitute a 7-deazapurine;

each Y is independently either $=C(R^5)-$ or =N-, provided that there are no more than 3 of =N- in the aromatic ring bearing Y;

each Z is independently either $=C(R^4)-$ or =N-;

n is 0 to 4;

R^5 is independently selected from -H, halogen, -CN, $-NH_2$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-S(O)_{0-2}R^7$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)R^7$, $-N(R^6)CO_2R^7$, $-C(O)R^6$,

optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; and

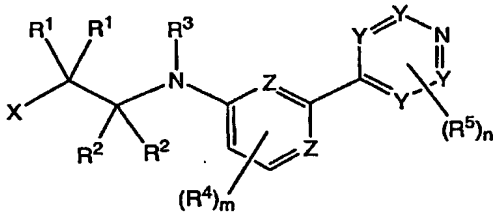
optionally two adjacent R^5's, together with the two carbons to which they are attached, form an eighth ring system fused with the aromatic ring system to which said two adjacent R^5's are attached as in formula I, said eighth ring system comprising between 5 and 7 atoms and substituted with 0 to 3 additional of R^5;

R^6 is -H or R^7; and

R^7 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

R^6 and R^7, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl ring, said optionally substituted five- to seven-membered heterocyclyl ring optionally containing at least one additional heteroatom selected from N, O, S, and P.

2. The compound according to claim 1, of formula II,

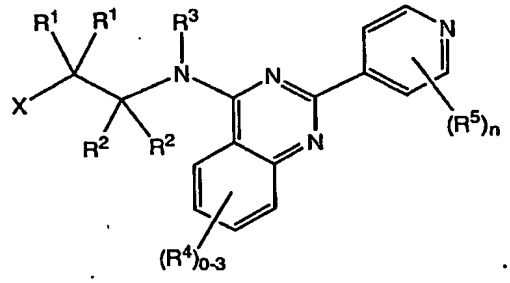
II 

3. The compound according to claim 2, wherein at least one of Z is –N=.

4. The compound according to claim 3, wherein Z is -N=.

5. The compound according to claim 4, wherein Y is =C(R^5)-.

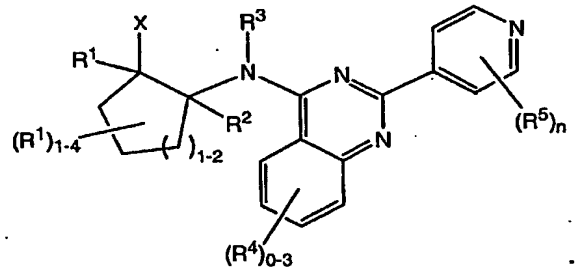
6. The compound according to claim 5, of formula III,

III 

7. The compound according to claim 6, wherein one each of R^1 and R^2, together with the corresponding carbons to which they are attached, form said first ring system, said first ring system comprising a saturated ring, said saturated ring optionally substituted with between 0 and 4 additional of R^1.

8. The compound according to claim 7, wherein said saturated ring is carbocyclic.

9. The compound according to claim 8, of formula IV

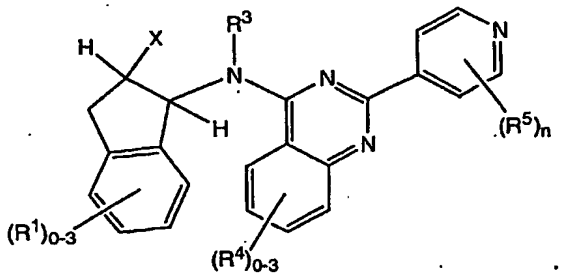
IV 

10. The compound according to claim 9, wherein X is selected from $-OR^6$, $-SR^6$, and $-N(R^6)R^7$.

11. The compound according to claim 10, wherein two of R^1, together with the carbon or carbons to which they are attached, form said second ring system.

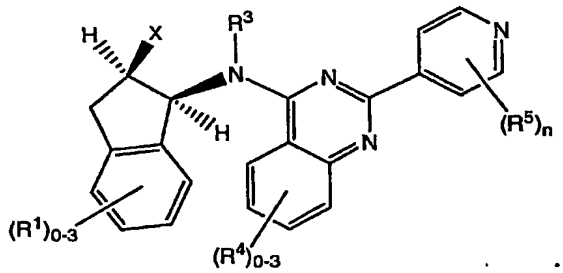
12. The compound according to claim 11, wherein said second ring system is a six-membered aryl ring system, fused with said first ring system, said second ring system optionally substituted with between 0 and 3 of R^1.

13. The compound according to claim 12, of formula V,

V 

14. The compound according to claim 13, wherein X is -OR^6.

15. The compound according to claim 14, of formula VI,

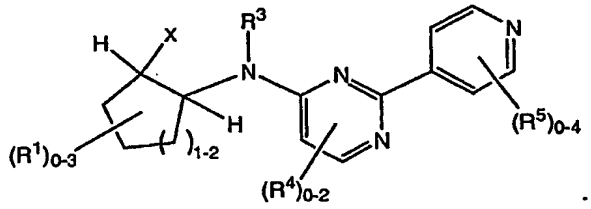
VI 

16. The compound according to claim 15, wherein R^3 is -H.

17. The compound according to claim 16, wherein X is -OH.

18. The compound according to claim17, wherein R^1, R^4, and R^5 are -H.

19. The compound according to claim 5, of formula VII,

VII 

20. The compound according to claim 19, wherein X is selected from -OR^6, -SR^6, and -$N(R^6)R^7$.

21. The compound according to claim 20, wherein X is -OH.

22. The compound according to claim 21, wherein R^3 is -H.

23. The compound according to claim 22, wherein at least one of R^1 is an optionally substituted aryl.

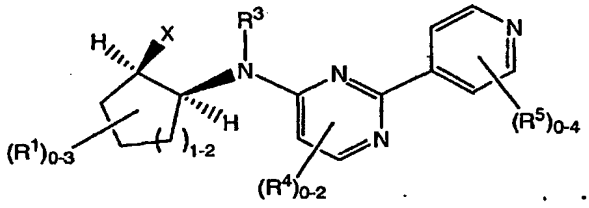
24. The compound according to claim 22, wherein at least one of R^4 is an optionally substituted aryl.

25. The compound according to claim 22, wherein at least one of R^1 is an optionally substituted phenyl.

26. The compound according to claim 22, wherein at least one of R^4 is an optionally substituted phenyl.

27. The compound according to claim 22, of formula **VIII**,

VIII



28. The compound according to claim 20, wherein two R^4's, together with the aromatic ring atoms to which they are attached, form said seventh ring system, said seventh ring system comprising between 0 and 2 nitrogens.

29. The compound according to claim 28, wherein said seventh ring system is substituted with between 0 and 3 additional of R^4.

30. The compound according to claim 1, selected from the compounds in Table 1.

Table 1

#	Name
1	N-cyclohexyl-2-pyridin-4-ylquinazolin-4-amine
2	2-pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)quinazolin-4-amine
3	N-cyclopentyl-2-pyridin-4-ylquinazolin-4-amine
4	N-(cyclohexylmethyl)-2-pyridin-4-ylquinazolin-4-amine

#	Name
5	2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
6	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
7	N-[(4-fluorophenyl)methyl]-2-pyridin-4-ylquinazolin-4-amine
8	N,N-dimethyl-N'-(2-pyridin-4-ylquinazolin-4-yl)ethane-1,2-diamine
9	N-(2,3-dihydro-1H-inden-1-yl)-2-pyridin-4-ylquinazolin-4-amine
10	N-(2-morpholin-4-ylethyl)-2-pyridin-4-ylquinazolin-4-amine
11	4-[4-(2-pyridin-4-ylquinazolin-4-yl)piperazin-1-yl]phenol
12	2-pyridin-4-yl-N-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine
13	4-piperazin-1-yl-2-pyridin-4-ylquinazoline
14	1,1-dimethylethyl 4-(2-pyridin-4-ylquinazolin-4-yl)piperazine-1-carboxylate
15	2-pyridin-4-yl-N-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]quinazolin-4-amine
16	4-[(1S)-2,3-dihydro-1H-inden-1-ylmethyl]-2-pyridin-4-ylquinazoline
17	(1R,2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
18	(1S,2R)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
19	1,1-dimethylethyl 4-[(2-pyridin-4-ylquinazolin-4-yl)amino]piperidine-1-carboxylate
20	2-pyridin-4-yl-N-{[2,4,6-tris(methyloxy)phenyl]methyl}quinazolin-4-amine
21	N-piperidin-4-yl-2-pyridin-4-ylquinazolin-4-amine
22	N-{(1S,2S)-2-[(phenylmethyl)oxy]cyclopentyl}-2-pyridin-4-ylquinazolin-4-amine
23	N-phenyl-N'-(2-pyridin-4-ylquinazolin-4-yl)benzene-1,4-diamine
24	3-[(2-pyridin-4-ylquinazolin-4-yl)amino]naphthalen-2-ol

#	Name
25	N-{4-[(1-methylethyl)oxy]phenyl}-2-pyridin-4-ylquinazolin-4-amine
26	(1S,2R)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
27	(1R,2S)-1-[(2-phenylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
28	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclopentanol
29	(1R,2R)-2-[(2-phenylquinazolin-4-yl)amino]cyclohexanol
30	(1S,2R,3R,5R)-3-(hydroxymethyl)-5-[(2-phenylquinazolin-4-yl)amino]cyclopentane-1,2-diol
31	(1S,2R)-1-[(6-chloro-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
32	N-(2-piperazin-1-ylethyl)-2-pyridin-4-ylquinazolin-4-amine
33	(1S,2R)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
34	(1R,2S)-1-[(2-pyridin-3-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
35	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclopentanol
36	(1R,2R)-2-[(2-pyridin-3-ylquinazolin-4-yl)amino]cyclohexanol
37	(1S,2R)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
38	(1R,2S)-1-[(2-pyridin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
39	(2S)-3-[(2-pyridin-4-ylquinazolin-4-yl)amino]propane-1,2-diol
40	[(2S)-1-(2-pyridin-4-ylquinazolin-4-yl)-2,3-dihydro-1H-indol-2-yl]methanol
41	(2R)-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
42	(2S)-1-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-2-ol
43	(1S,2R)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
44	(1R,2S)-1-{[2-(2-ethylpyridin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol

#	Name
45	(1S,2R)-1-[(6-bromo-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
46	(1S,2R)-1-{[6,7-bis(methyloxy)-2-pyridin-4-ylquinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
47	1-(2-pyridin-4-ylquinazolin-4-yl)piperidin-3-ol
48	(1S,2R)-1-{[2-pyridin-4-yl-7-(trifluoromethyl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
49	(1S,2R)-1-({2-[6-(methyloxy)pyridin-3-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol
50	N-[(3S)-piperidin-3-yl]-2-pyridin-4-ylquinazolin-4-amine
51	(1S,2R)-1-[(7-methyl-2-pyridin-4-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
52	(1S,2R)-1-({2-[2,4-bis(methyloxy)pyrimidin-5-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol
53	(2R)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol
54	(2S)-3-methyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]butan-1-ol
55	(2S)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
56	(2R)-2-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
57	(1S,2R)-1-[(2-pyridin-4-ylpyrimidin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
58	(1S,2R)-1-[(2-pyrazin-2-ylquinazolin-4-yl)amino]-2,3-dihydro-1H-inden-2-ol
59	(1S,2R)-1-{[2-(4-aminopyridin-3-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
60	(2R)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
61	(2S)-3-phenyl-2-[(2-pyridin-4-ylquinazolin-4-yl)amino]propan-1-ol
62	2-[(phenylmethyl)(2-pyridin-4-ylquinazolin-4-yl)amino]ethanol
63	(1S,2R)-1-{[2-(2-aminopyrimidin-4-yl)quinazolin-4-yl]amino}-2,3-dihydro-1H-inden-2-ol
64	5-(4-{[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}quinazolin-2-yl)pyridin-2-ol

#	Name
65	(1S,2R)-1-({2-[2-(methylthio)pyrimidin-4-yl]quinazolin-4-yl}amino)-2,3-dihydro-1H-inden-2-ol

31. A pharmaceutical composition comprising a compound according to any one of claims 1-30 and a pharmaceutically acceptable carrier.

32. A metabolite of the compound or the pharmaceutical composition according to any of claims 1-31.

33. A method of treating a kinase-dependent disease or condition comprising administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 31.

34. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the pharmaceutical composition according to claim 31.

35. The method according to claim 34, wherein the kinase is Tie-2.

36. The method according to claim 35, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

ABSTRACT

The present invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Compounds of the invention inhibit, regulate and/or modulate kinases, particularly Tie-2. Methods of using the compounds and pharmaceutical compositions thereof to treat kinase-dependent diseases and conditions are also an aspect of the invention.

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